Stereoselective synthesis of (E)-trisubstituted acid derivatives

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Stereoselective Synthesis of (*E*)-Trisubstituted Acid Derivatives

submitted by Frédéric Feuillet

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Abstract

This PhD thesis describes on my progress towards the application of the aldol/*retro*-aldol reaction to the development of a *novel* concept for using chiral auxiliaries for the asymmetric synthesis of chiral aldehyde fragments. As a result of these investigations I have discovered synthetic methodology that employs *syn*-β-hydroxy-*N*-acyloxazolidin-2-ones as substrates for a *novel* intramolecular cyclisation/elimination reaction to afford trisubstituted *(E)*-α,β-unsaturated amides in high d.e. In Chapter 1 the range of strategies that are commonly employed to obtain chiral molecules in enantiopure form are described. The concept of directed reactions as a tool for introducing new chiral centres to a chiral synthon is explained, and a few relevant examples are described in a non-exhaustive fashion. In Chapter 2 the literature published on the synthesis of trisubstituted *(E)*- and *(Z)*-α,β-unsaturated carboxylic acids derivatives is comprehensively reviewed concentrating on examples that have been recently employed for natural product synthesis. In Chapter 3, the original chiral auxiliary concept based on the potential of the aldol/*retro*-aldol reaction to form/cleave stereogenic hydroxyl centres and the capacity of hydroxyl group to direct reactions at prochiral centres is discussed. The preliminary reactions that were carried out towards this aim that led to the discovery of *novel* methodology for the stereoselective synthesis of *(E)*-trisubstituted acid derivatives are also described. In Chapter 4 the scope and limitation of the methodology for affording trisubstituted *(E)*-α,β-unsaturated amides in 67-99% yield and in 90 to > 95% d.e. is described, although lower stereoselectivities were observed with *syn*-aldolates that contained γ,δ-unsaturation. A range of these *(E)*-amides were then cleanly transformed into their corresponding carboxylic acids and oxazolines in high yield. In Chapter 5 the mechanism of the novel elimination reaction is explored and found to occur *via* a tandem rearrangement/E1cB elimination reaction. 1,3-Oxazinane-2,4-dione intermediates were isolated, and the mechanism is discussed in the light of the results arising from Chapter 4. In Chapter 6, it was demonstrated that a series of *syn*- and *anti*-aldolates derived from chiral aldehyde fragments, heteroaryl aldehydes, and *N*-acyloxazolidine-2-ones that contain heteroatom substituents at their α-position, also undergo stereoselective elimination to afford *(E)*-amides However, products arising from a competing *retro*-aldol reaction were isolated in a number of cases. In Chapter 7, suitable aldolate substrates that undergo clean *retro*-aldol reaction were identified, thus establishing conditions that enabled a *novel* concept for employing chiral auxiliaries for the enantioselective synthesis of aldehydes to be realised.

Acknowledgements

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And a huge thanks to all of my friends, those I have met in England and the others, who all contributed to make these last few years as great as they could be. I don't feel like naming but I'll give it a go anyway: The French triplettes (Marie, Selma, Karine and Christelle, well they are 4!), Le Club des Cinq (Jérôme, Anthony, Steph and Julie), Olivier, Tim, Florence, Claire, Popi, Didier, Adem, Gerta, Yolanda, Mike and how could I have forgotten the ever so cheeky (!) Koko. This list is not exhaustive (☺ I am of course thinking about Carole who would go to such an extent to make me smile, Sylvie, David, ...).

And finally, last but not the least, ... à Maman, Papa et ma "petite" soeur Delphine. Cette thèse est dédiée à mes grands-parents.

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Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonanyl
BINAP	2,2'-*bis*-(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
^{n}Bu, Bu	butyl
^{t}Bu	*tert*-butyl
cat	catalyst
Cbz	carboxybenzyl
CI	chemical ionisation
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
Δ	heat
DAST	diethylaminosulfur trifluoride
dba	dibenzylidene acetone
d.e.	diastereomeric excess
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropylcarbodiimide)
ee	enantiomeric excess
EI	electron impact
eq.	equivalent
ES	electrospray

Et	ethyl
FAB	fast atom bombardment
fur-H	furane
HIV	human immunodeficiency virus
HWE reaction	Horner-Wadsworth-Emmons reaction
ind-H	indole
IR	infra-red
KHMDS	potassium hexamethyldisilazide
m	multiplet
Me	methyl
min	minute
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m-CPBA	*meta*-chloroperoxybenzoic acid
mp	melting point
Ms	methanesulfonyl, mesyl
m/z	mass / charge
NaHMDS	sodium hexamethyldisilazide
NMR	Nuclear Magnetic Resonance
Ph	phenyl
ppm	parts per million
^{n}Pr, Pr	propyl
^{i}Pr	^{iso}-propyl
Pyr-H	pyridine
q	quartet
rt	room temperature
s	sharp
T	temperature
Tf	trifluoromethanesulfonyl, triflyl
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl, tosyl

CHAPTER 1. Asymmetric Synthesis in Organic Synthesis

1.1 Introduction

The reactivity of organic compounds is closely related to their three-dimensional structure. For example the biological properties of all chiral organic molecules depends on their stereochemistry, with important implications for drugs, insecticides, plant growth regulators, perfumery and flavouring compounds.[1]

Thalidomide is a good example of the potential problems associated with the administration of racemic drugs. It was prescribed as a racemic mixture for many years in order to relieve pregnant women from pain and nausea, before it was realised in the 1960's that the desired activity resided in the *(R)*-**1** enantiomer, whilst the *(S)*-**1** enantiomer was teratogenic leading to tragically malformed infants (Figure 1).[2]

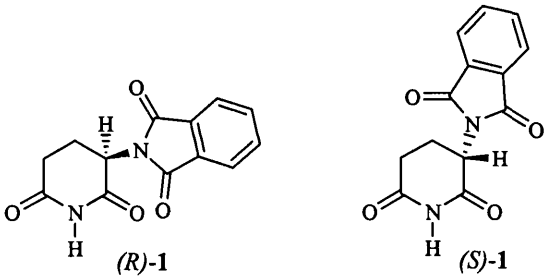


Figure 1

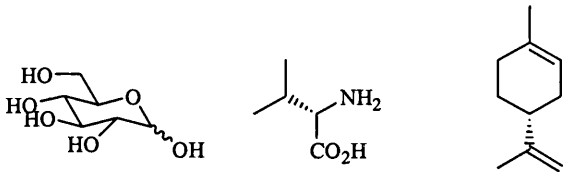
One of the great challenges within organic chemistry lies in the synthesis of naturally occurring molecules that contain one or more stereogenic centres.[3] As a consequence, a great deal of effort has been directed towards the development of methodology that allows chiral molecules to be constructed in a stereoselective manner.[4] The syntheses of most complex molecules relies on a strategy where the stereogenic centres of one or more small chiral building blocks are used to control the introduction of new stereogenic centres into the target molecule *via* a series of stereoselective reactions.[5] Access to a wide range of these small chiral templates is therefore critical, and as a consequence a number of different approaches have been developed for their preparation.

1.2 Preparation of Enantiopure Synthons

There are a number of different strategies employed to obtain chiral molecules in enantiopure form. These different approaches may be conveniently divided into three main categories; (i) the use of molecules available from the chiral pool; (ii) the resolution of racemates; (iii) asymmetric synthesis.

1.3 The Chiral Pool

This approach employs naturally occurring enantiomerically pure substrates that are readily available from Nature as chiral templates for synthesis. For example, naturally occurring carbohydrates such as *D*-glucose **2**, or α-amino acids such as *L*-valine **3** have been used widely in synthesis. Alternatively, chiral secondary metabolites such as the terpene limonene **4** are often available in multigram quantities (Figure 2).



2 **3** **4**

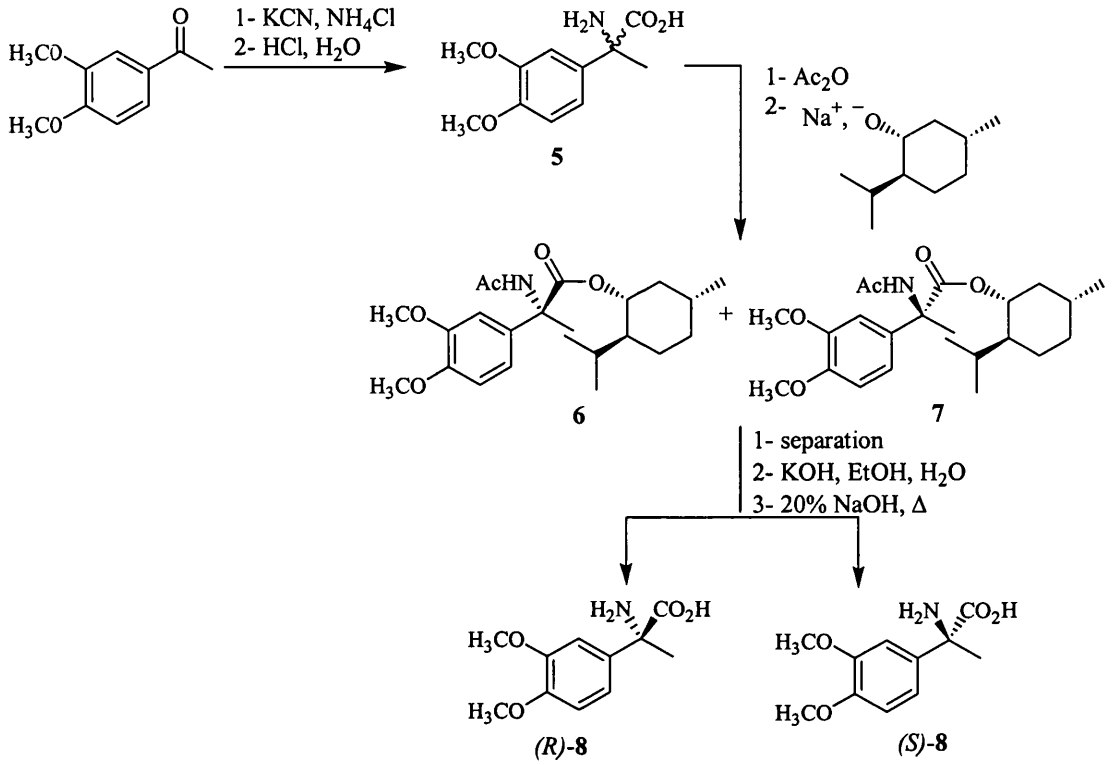
Figure 2

There are problems with this approach however. Supply is often limited by availability, whilst only one enantiomeric series may occur naturally. For example, many α-amino acids are only available in their proteinogenic *L*-series, whilst carbohydrates are generally *D*-configured. Additionally, lengthy synthetic steps are often required to remove redundant functionality from naturally occurring substrates containing more than one stereogenic centre.

1.4 Resolution of Racemates

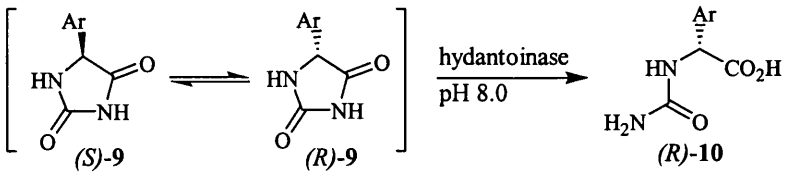
Techniques have been developed to obtain compounds as single enantiomers from racemic mixtures *via* resolution. This approach allows the use of racemic starting materials for the preparation of enantiopure compounds for synthesis. For example, the racemic α-methyl-α-amino acid **5** was treated with the sodium salt of enantiomerically pure menthol to give two diastereoisomers of the ester **6** and **7**. Fractional crystallisation of the resulting mixture enabled one of the diastereoisomers **6** to be obtained in pure crystalline form, while the

other diastereoisomer **7** remained in solution. **7** could be obtained in isomerically pure form *via* subsequent recrystallisation of the mother liquors. Hydrolysis of either diastereoisomer **6** or **7** afforded either the *(R)*-**8** or *(S)*-**8** enantiomer of the parent α-amino acid in enantiopure form respectively (Scheme 1).[6]



Scheme 1

The key problem associated with resolution is the fact that the maximum theoretical yield of each pure enantiomer obtainable is 50%. A number of elegant dynamic kinetic resolution procedures have been developed to address this issue in which the racemic substrate rapidly racemises under the reaction conditions. For example, the stereogenic centre of racemic hydantoin **9** is acidic and rapidly racemises at pH 8.0, enabling hydantoinase enzyme to catalyse quantitative hydrolysis of the *(R)*-**9** enantiomer to afford *(R)*-*N*-carbamoyl-α-amino-acid **10** in high e.e. (Scheme 2).[7]



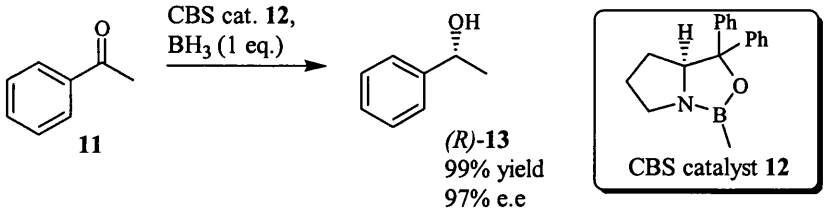
Scheme 2

1.5 Asymmetric Synthesis

Asymmetric synthesis may be defined as the conversion of a prochiral unit into a chiral unit in such a way that the stereoisomeric products are formed in unequal amounts. To achieve asymmetric induction, one component of a reaction must be chiral. This ensures that the possible transition states of the reaction are diastereoisomeric, and potentially of different energies. If the diastereomeric transition states differ significantly in energy then high stereoselectivity should be observed for a given reaction. In the absence of a chiral component, the possible transition states are enantiomeric, thus of equal energy, and therefore lead to a racemate. Following this basic principle, the strategies for asymmetric induction may be conveniently classified into three main approaches, asymmetric catalysis, chiral reagents, and the use of chiral auxiliaries.

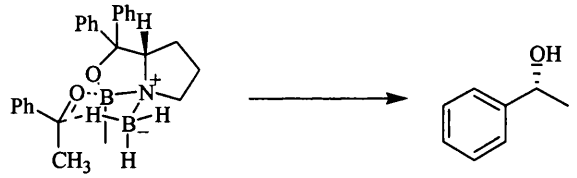
1.5.1 Asymmetric Catalysis

Chiral information is transferred in the transition state of a reaction using a chiral catalytic species that binds reversibly to both a substrate and an achiral reagent, thus facilitating reaction in a diastereoselective manner. For example, borane does not reduce ketones to alcohols in the absence of a catalyst, however with a catalytic amount (10%) of the CBS (Corey, Bakshi, and Shibita) oxazaborolidine catalyst **12**, it can reduce acetophenone **11** to secondary alcohol **13** in high e.e. using a stoichiometric amount of achiral borane as hydride source (Scheme 3).[8]



Scheme 3

Thus, when acetophenone **11** is complexed to the boron atom of oxazaborolidine **12**, it becomes electrophilic enough to be reduced by a weak hydride source, which is delivered *via* the six-membered cyclic transition state **14**. The observed facial selectivity arises from the preference of the larger phenyl group, to occupy a pseudoequatorial conformation in the transition state (Figure 3).



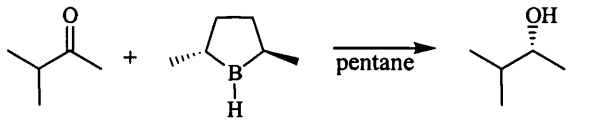
14 *(R)*-**13**

Figure 3

Whilst a large number of chiral catalysts have been developed, only a limited number have entered mainstream synthetic organic chemistry primarily due to problems associated with substrate selectivity and catalyst turnover. Thus, small changes in substrate structure can often lead to the catalyst forming mixtures of enantiomeric products that are difficult to purify to homogeneity.

1.5.2 Chiral Reagents

This approach is similar to the asymmetric catalytic approach described in Section 1.5.1 however in this case a stoichiometric quantity of a chiral reagent is used for the stereoselective transformation of an achiral substrate. For example, ketone **15** may be reduced by the chiral borane **16** to afford *(R)*-alcohol **17** in >99% e.e. (Scheme 4).[9]



15 **16** *(R)*-**17**
> 99% e.e.

Scheme 4

Whilst this approach is often a highly efficient one the cost of employing stoichiometric quantities of chiral reagents is often prohibitive.

1.5.3 The Chiral Auxiliary Approach

The chiral auxiliary approach relies on a strategy involving attachment of a chiral auxiliary **CA** to a prochiral substrate **S** resulting in the formation of a **CA-S** complex (Figure 4). Subsequent derivatisation of the **CA-S** complex, under the stereodirecting control of the chiral auxiliary fragment, results ideally in the formation of single diastereoisomer **CA-P** containing one or more new stereogenic centres. If stereocontrol is incomplete then any minor diastereoisomer must be removed *via* recrystallisation or chromatography. Finally,

the diastereoisomerically pure **CA-P** product is cleaved to afford the enantiomerically pure product **P**, and the chiral auxiliary fragment **CA** which may then be recycled as required.

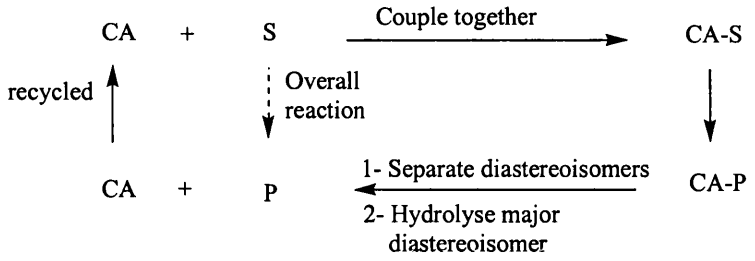
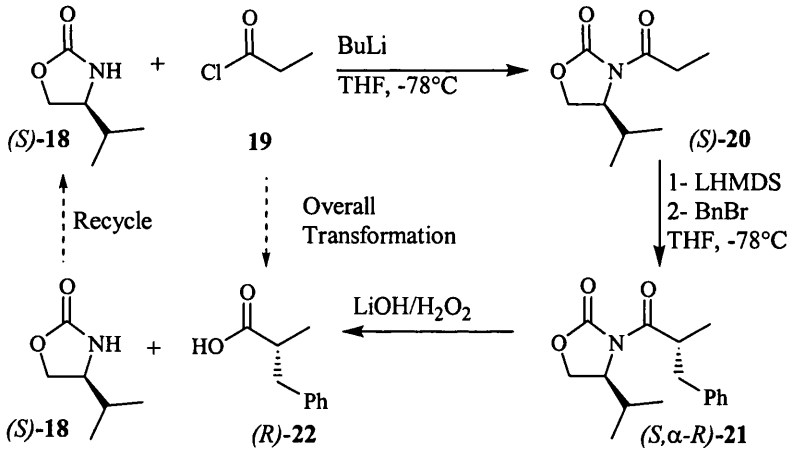


Figure 4

This principle may be illustrated by considering the use of Evans' oxazolidin-2-one **18** for the asymmetric synthesis of chiral α-substituted acid fragments. The oxazolidinone chiral auxiliary **18** is first attached to the achiral acid fragment **19** to afford *N*-propionyl-4-isopropyloxazolidin-2-one **20**. Deprotonation of **20** with LHMDS in THF at –78°C affords a chelated (*Z*)-enolate that reacts with an incoming electrophile on the opposite face to the stereodirecting *iso*-propyl group to afford the major diastereoisomer **21** in > 95% d.e. Purification of **21** to homogeneity, followed by alkaline cleavage with lithium hydroperoxide, affords enantiopure *(R)*-benzylpropanoic acid **22** and the chiral auxiliary oxazolidin-2-one **18** (Scheme 5).[10]



Scheme 5

Once again, the use of chiral auxiliaries for asymmetric synthesis is not without its problems however. These include the need to use stoichiometric quantities of expensive chiral auxiliaries; lengthy synthetic protocols for attaching and detaching the chiral auxiliary fragment; and the fact that on cleavage the chiral auxiliary must be separated from the chiral product.

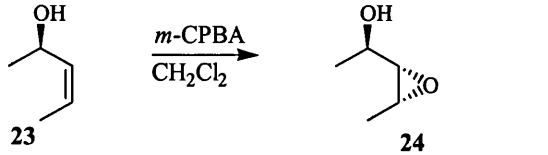
1.6 Directed Reactions

Once a suitable route to a chiral synthon has been identified then it must be synthetically elaborated to afford the desired target chiral molecule *via* a series of stereoselective reactions that often rely on the presence of existing stereocentres to induce asymmetry. As a consequence of their natural abundance within the structure of a wide range of natural products, a significant number of 'directed' reactions have been developed that employ stereogenic hydroxyl groups to control the stereoselective functionalisation of sp^2 centres in high d.e.[5] These hydroxyl directed transformations include protocols for the stereoselective epoxidation, cyclopropanation and hydrogenation of allylic alcohols and these approaches are discussed in brief in the following section.

1.6.1 Hydroxyl directed epoxidations

The stereoselective epoxidation of allylic alcohols is commonly achieved in a diastereoselective manner using either *meta*-chloroperoxybenzoic acid (*m*-CPBA) or $VO(acac)_2/H_2O_2$ as epoxidising agents. The hydroxyl group directs stereoselective epoxidation in both cases, however facial selectivity is achieved *via* a different mechanism in each case.

For example, *m*-CPBA epoxidised 1,2-disubstituted alkene **23** to afford α,β-epoxyalcohol **24** in high d.e. (Scheme 6).[11,12,13] The stereoselectivity of this directed epoxidation was rationalised through transition state **25** in which an electron lone pair on the peracid oxygen atom being transferred to the alkene forms a hydrogen bond with the hydrogen atom of the allylic hydroxyl functionality. As a result the oxygen atom was delivered on the same face as the hydroxyl group and the reaction affords a *syn*-epoxide in high d.e. (Figure 5).[14]



23 **24**

diastereoselection > 95:5

Scheme 6

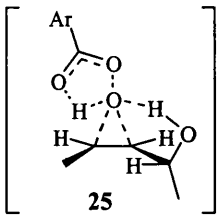
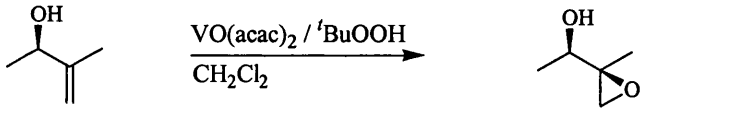


Figure 5

In a comparative study, $VO(acac)_2$ was also shown to catalyse efficiently the epoxidation of 1,1-disubstituted alkene **26** to afford the *syn*-α,β-epoxyalcohol **27** stereoselectively (Scheme 7).[11] Unlike *m*-CPBA however, the mechanism of this epoxidation was proposed to proceed *via* transition state **28** in which initial coordination of the vanadium metal to the oxygen lone-pair of the allylic alcohol resulted in the oxygen atom of the coordinated ^{t}BuOO- fragment being delivered to the olefin (Figure 6).



(2R)-**26** *(2R,3S)*-**27**
diastereoselection > 95:5

Scheme 7

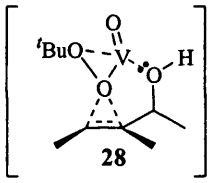
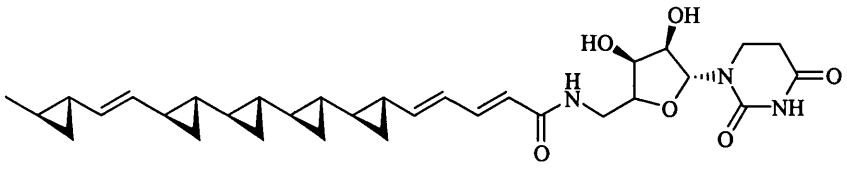


Figure 6

1.6.2 Cyclopropanation

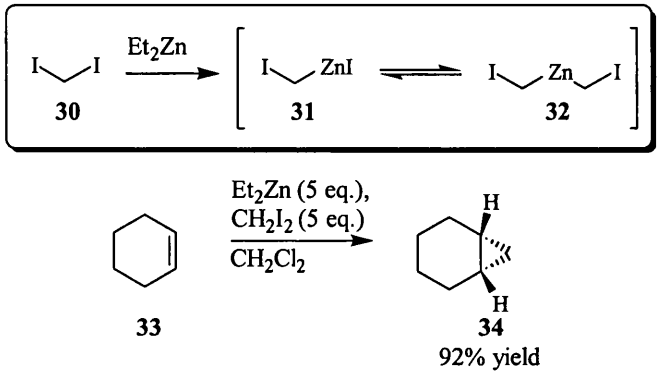
A number of natural products and biologically active compounds contain cyclopropane rings, for example the antifungal antibiotic jawsamycin **29**, which was first synthesised in 1996 (Figure 7).[15]



FR-900848 or jawsamycin **29**

Figure 7

The most important route for the introduction of the cyclopropane functionality was discovered by Simmons and Smith involving the use of Zn/Cu couple and CH_2I_2 **30** to generate a zinc carbenoid species for the functionalisation of alkenes.[16] This procedure has been superceded by the use of diethylzinc to generate a carbenoid equivalent comprised of both the monomeric **31** and the dimeric species **32** that readily underwent addition to olefin **33** to produce a cyclopropane **34** (Scheme 8).[17]



Scheme 8

Importantly, the presence of a hydroxyl group in the allylic position of the alkene increased the rate of cyclopropanation whilst also introducing diastereocontrol into the reaction. This was achieved *via* coordination of the lone pair of the hydroxyl group to the zinc atom of the carbenoid thus delivering the carbene to the alkene according to the transition state model **35** described in Figure 8.

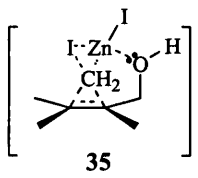
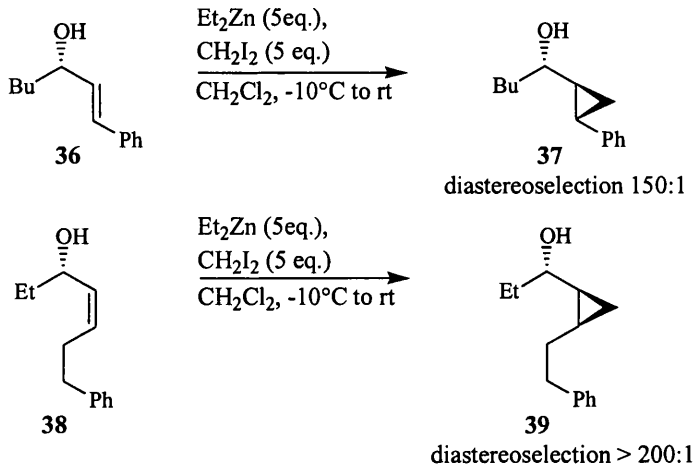


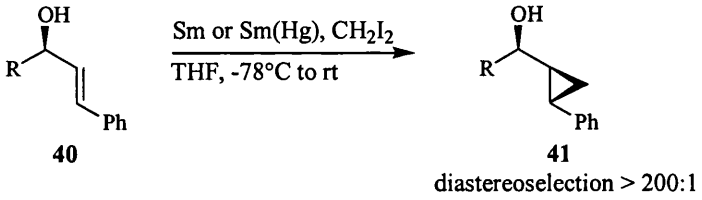
Figure 8

Charette *et al.* demonstrated that Et_2Zn/CH_2I_2 affords the best results for these type of hydroxyl directed cyclopropanations.[18] From an optimised 1:1 ratio of reagent and carbenoid they found that the cyclopropanation of allylic alcohols *cis*-**36** and *trans*-**38** afforded *syn*-**37** and *syn*-**39** as the major stereoisomers respectively (Scheme 9).



Scheme 9

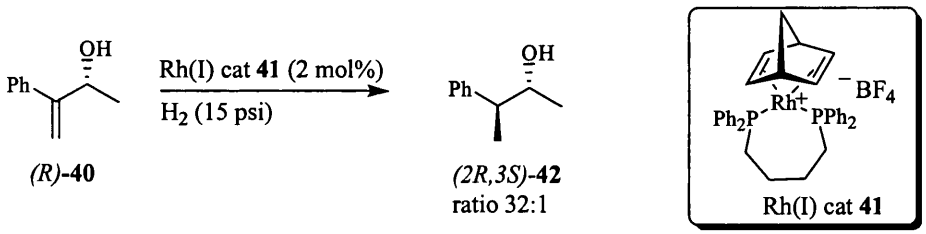
Samarium-derived carbenoids offer a mild alternative to the Simmons-Smith reagent with the cyclopropanation reaction occuring at –60°C in a very stereoselective manner.[19] The *trans*-allylic alcohol **40** yielded the *syn*-α,β-cyclopropane alcohol **41** with excellent diastereoselectivity (Scheme 10).



Scheme 10

1.6.3 Hydrogenation of acyclic olefins

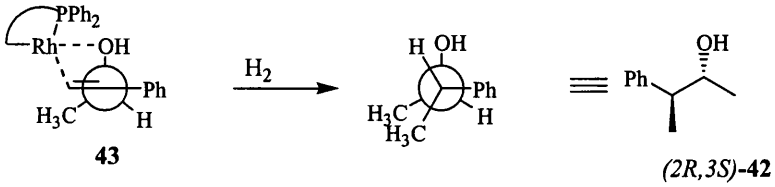
Hydrogenation of allylic alcohols in the presence of rhodium catalyst **41** consistently affords chiral alcohols that contain new stereogenic centres at their α-position in high d.e. For example, hydrogenation of 1,1-disubstituted alkene **40** afforded an alcohol **42** in which the newly formed methyl group was *anti* to the pre-existing hydroxyl group (Scheme 11).[20]



Scheme 11

The observed stereochemistry has been explained according to transition state **43** (Figure 9). The rhodium transition metal complexed to both the olefin and the oxygen functionality

of **40** to afford transition state **43**, that reacted with molecular hydrogen to afford an octahedral complex that subsequently delivered hydrogen to the alkene functionality to afford *anti*-alcohol **42** in high d.e.



43 *(2R,3S)*-**42**

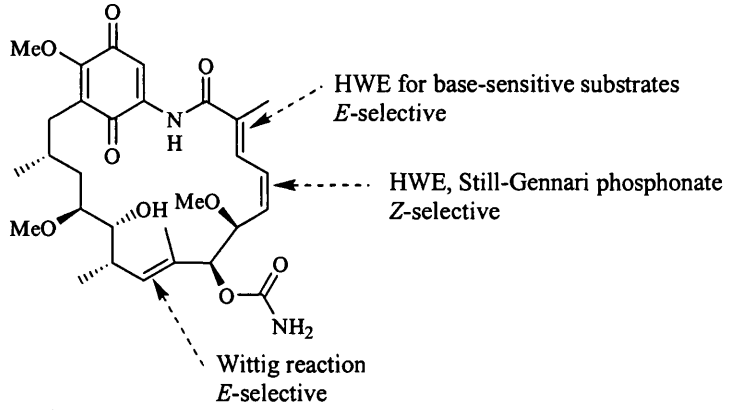
Figure 9

1.7 A new concept in chiral auxiliary design

I wished to devise a synthetic protocol that would combine the synthetic capacity of chiral auxiliaries to generate fragments that contain new stereogenic centres in high d.e. with the potential of directed reactions to control the stereoselective transformation of prochiral centres. The success of this project would afford a new concept in chiral auxiliary design, as well as providing novel methodology for the asymmetric synthesis of enantiopure aldehyde fragments. However, as a consequence of my studies directed towards this aim, a new diastereoselective approach to the synthesis of trisubstituted *(E)*-α,β-unsaturated amides has been discovered, and I will now review recent developments in methodologies that afford trisubstituted acid derivatives in high d.e.

CHAPTER 2. Review on the Stereoselective Synthesis of Electron-Deficient Alkenes

The importance of stereoselective methods to prepare unsaturated carbonyl compounds with either *(E)*- or *(Z)*- stereochemistry for natural product synthesis cannot be underestimated. Indeed, many natural products contain unsaturated carbonyl fragments whose *(E)*- or *(Z)*-geometry must be controlled if a successful synthesis is to be achieved. For example, (+)-geldanamycin **44** contains two trisubstituted *(E)*-alkene fragments and one disubstituted *(Z)*-alkene fragment (Figure 10).[21]



(+)-geldanamycin **44**

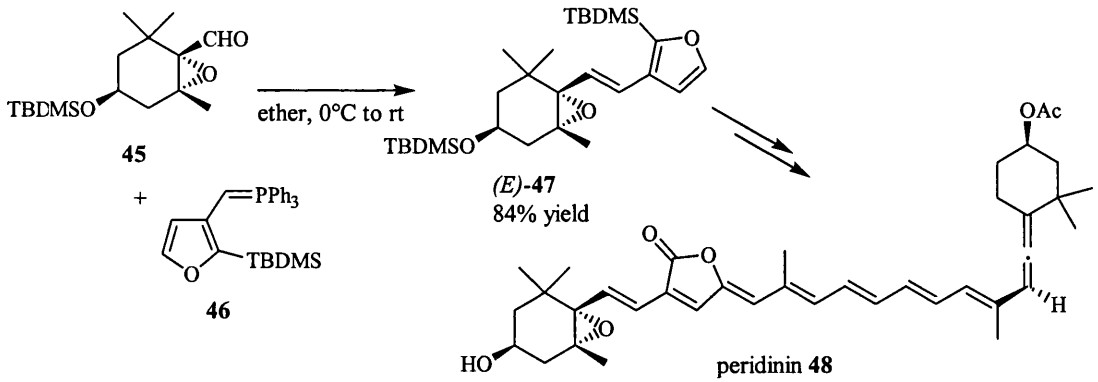
Figure 10

Given their importance, many procedures for the stereoselective synthesis of alkenes have been designed over the years for the stereoselective synthesis of natural products. Before describing specific approaches towards the synthesis of trisubstituted electron-deficient alkenes that are directly relevant to my research, it is instructive to consider briefly some established stereoselective protocols that have recently been employed for introducing highly functionalised alkene fragments into natural product targets.

2.1 General procedures towards the stereoselective synthesis of alkenes

2.1.1 The Wittig reaction

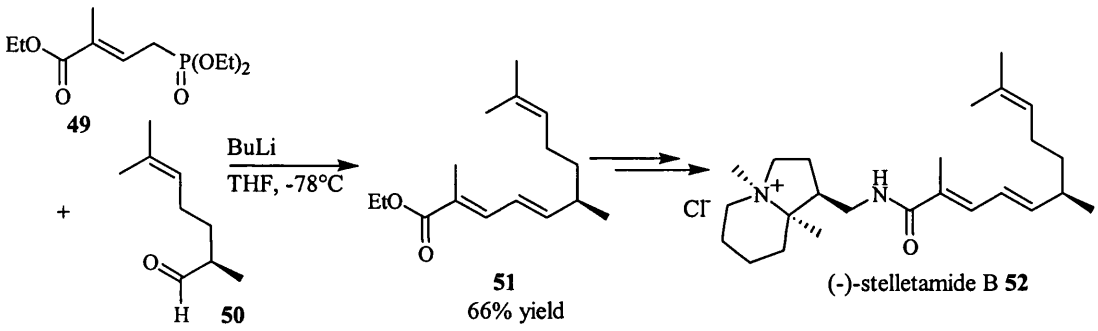
Katsumura *et al.* described a new route to peridinin in which a *novel* Wittig reagent **46** was successfully prepared from 3-furanmethanol and reacted with epoxyaldehyde **45** to afford the corresponding furan derivative *(E)*-**47** in excellent yield and as a single isomer, which was subsequently employed for the synthesis of the carotenoid peridinin (Scheme 12).[22]



Scheme 12

2.1.2 The Horner-Emmons reaction

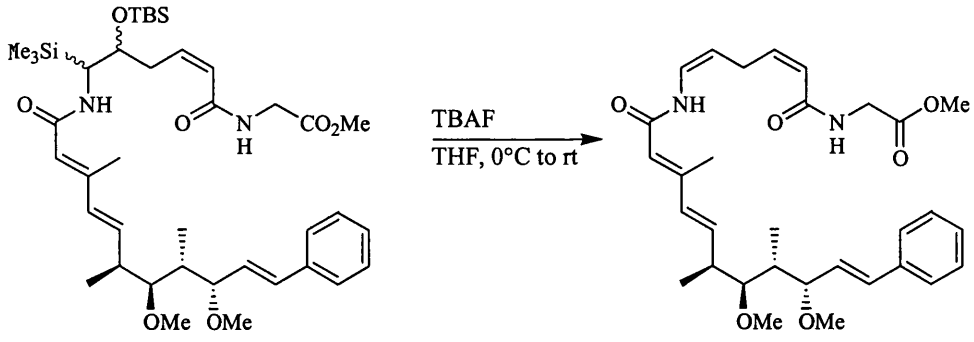
Kibayashi *et al.* described the first synthesis of antifungal natural product (-)-stelletamide B **52**, using reaction of the functionalised phosphonate ester **49** with α-substituted aldehyde **50** to afford **51** with good *(E)*-stereocontrol and retention of stereochemistry at the stereogenic centre (Scheme 13).[23]



Scheme 13

2.1.3 The Peterson olefination

Chakraborty *et al.* reported in 2003 the facile diastereoselective Peterson elimination reaction of β-hydroxysilane **53** under basic conditions with *(Z)*-stereocontrol to afford (+)-crocacin A **54** in good yield as the sole isomer (Scheme 14).[24]



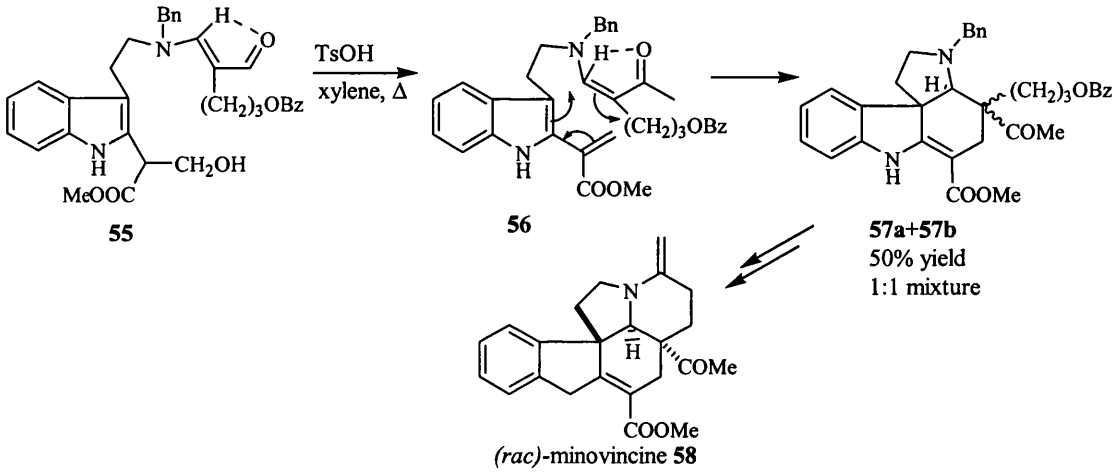
53

(+)-crocacin A
(Z)-**54**
86% yield

Scheme 14

2.1.4 Dehydration of alcohols

Kalaus, Szántay *et al.* reported an interesting cyclisation reaction for the synthesis of alkaloid (+/-)-minovincine **58**, involving dehydration of alcohol **55** to afford alkene **56**, which cyclised in a [4+2] cycloaddition fashion to give a 1:1 mixture of the epimers **57a** and **57b** (Scheme 15).[25]



55

56

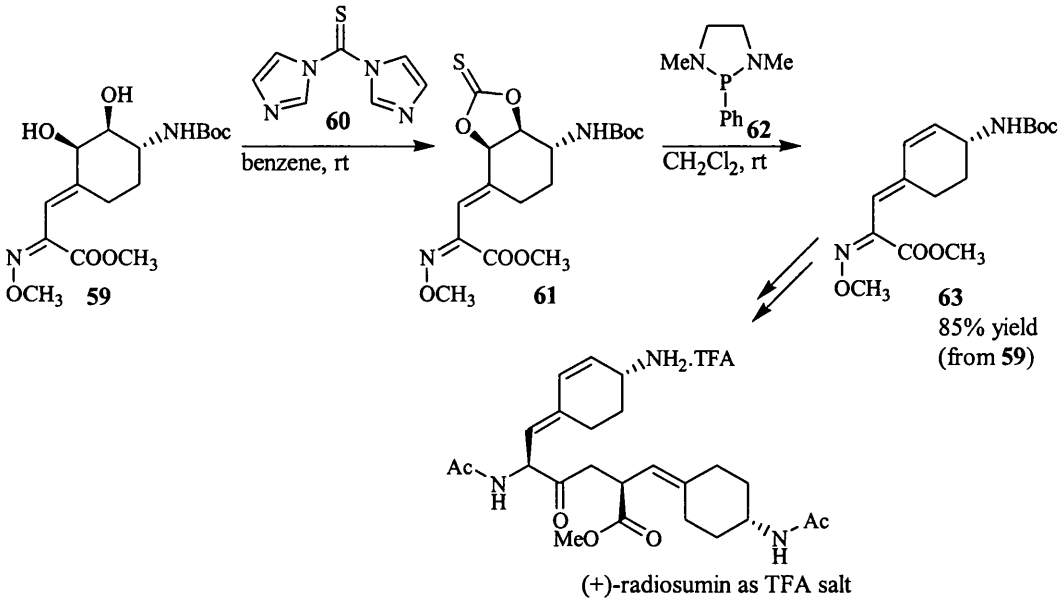
57a+57b
50% yield
1:1 mixture

(rac)-minovincine **58**

Scheme 15

2.1.5 The Corey-Winter olefination

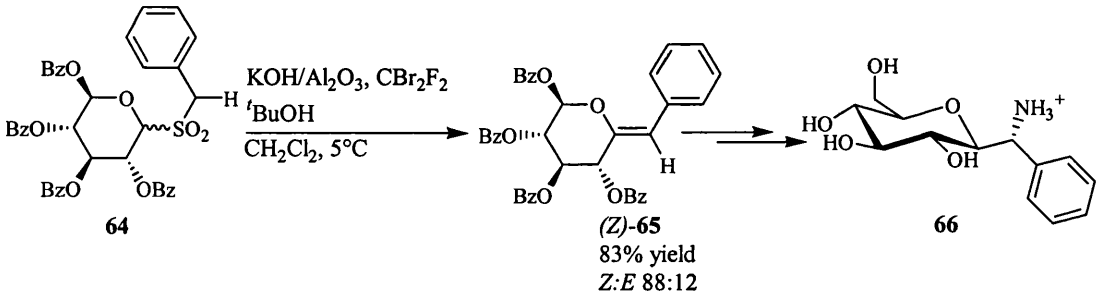
Aoyama, Shioiri *et al.* reported the use of the Corey-Winter protocol to introduce unsaturation into a functionalised cyclohexane. *syn*-Diol **59** was treated with 1,1'-thiocarbonyldiimidazole **60** to give thionocarbonate fragment **61** that smoothly gave diene **63** on treatment with the phospholidine **62** (Scheme 16).[26]



Scheme 16

2.1.6 The Ramberg-Backlund rerrangement

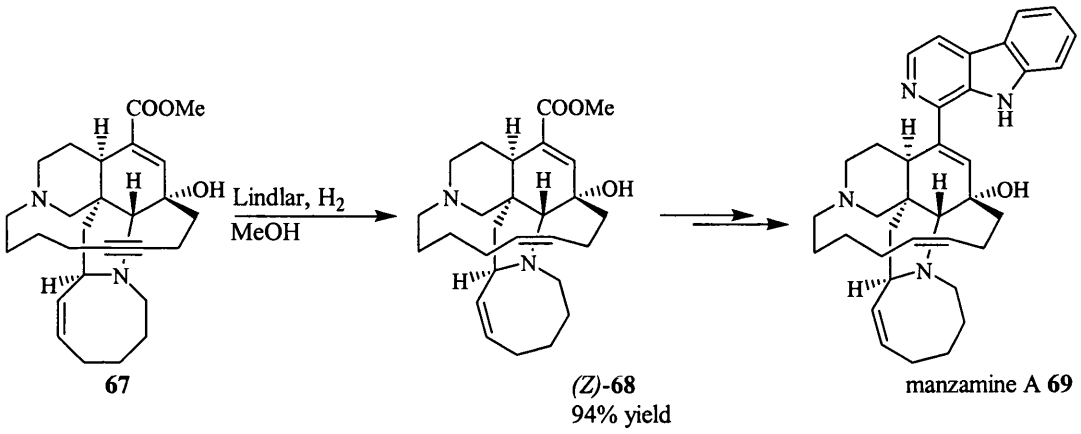
Taylor *et al.* reported the stereoselective synthesis of highly desirable *exo*-glycals *via* a tandem halogenation/Ramberg-Backlund rearrangement, in which glycosyl sulfone **64** was exposed to elimination conditions to afford *(Z)*-trisubstituted alkene **65** in high yield,[27] which was subsequently converted to novel β-glycosidase inhibitor **66** (Scheme 17).[28]



Scheme 17

2.1.7 Hydrogenation of alkynes

Winkler *et al.* has reported the hydrogenation of *(E)*-**67**, catalysed by Lindlar's catalyst to afford *(E,Z)*-alkene **68** quantitatively on his route towards the synthetically challenging polycyclic alkaloid manzamine A **69** (Scheme 18).[29]

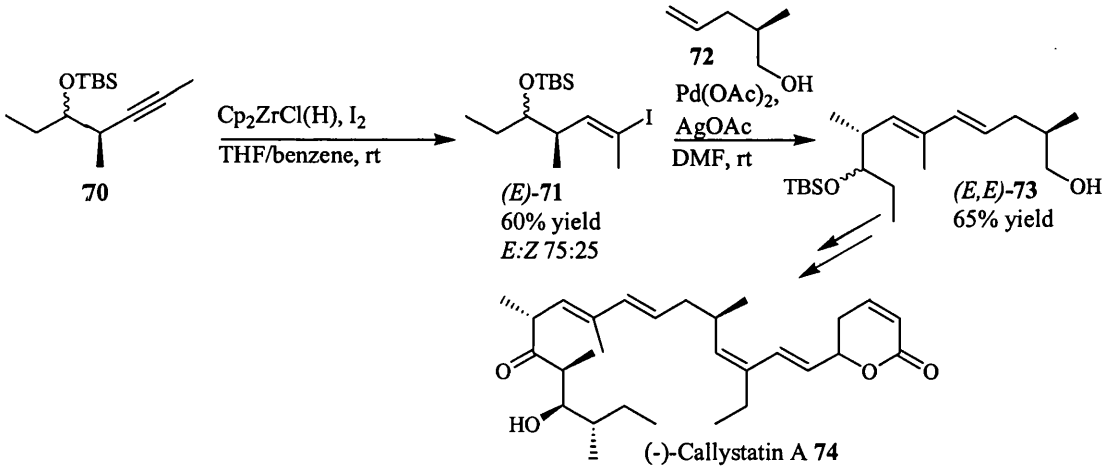


67 *(Z)*-68 94% yield manzamine A 69

Scheme 18

2.1.8 The Heck coupling

Kalesse *et al.* reported the enantioselective synthesis of callystatin A **74** in 2001, a key structural feature of which is the presence of the two-diene moieties. Treatment of alkyne **70** with Schwartz's reagent afforded an organozirconium species, which was quenched with I_2 to give vinyl iodide *(E)*-**71**. Subsequent coupling of vinyl iodide **71** and terminal alkene **72** was then carried out under Heck conditions to afford *(E,E)*-diene **73** in 65% yield (Scheme 19).[30]

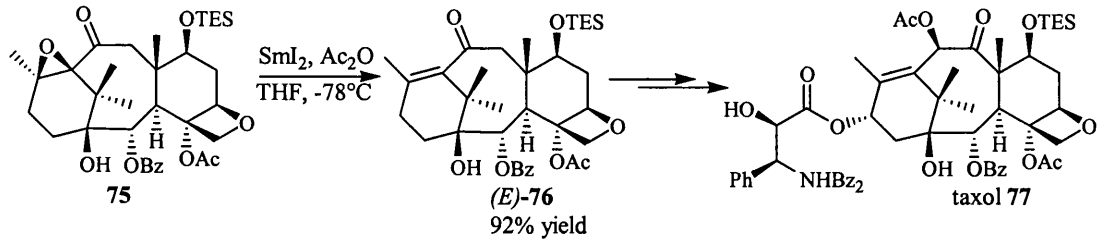


70 *(E)*-71 60% yield *E:Z* 75:25 *(E,E)*-73 65% yield (-)-Callystatin A 74

Scheme 19

2.1.9 Elimination of epoxides

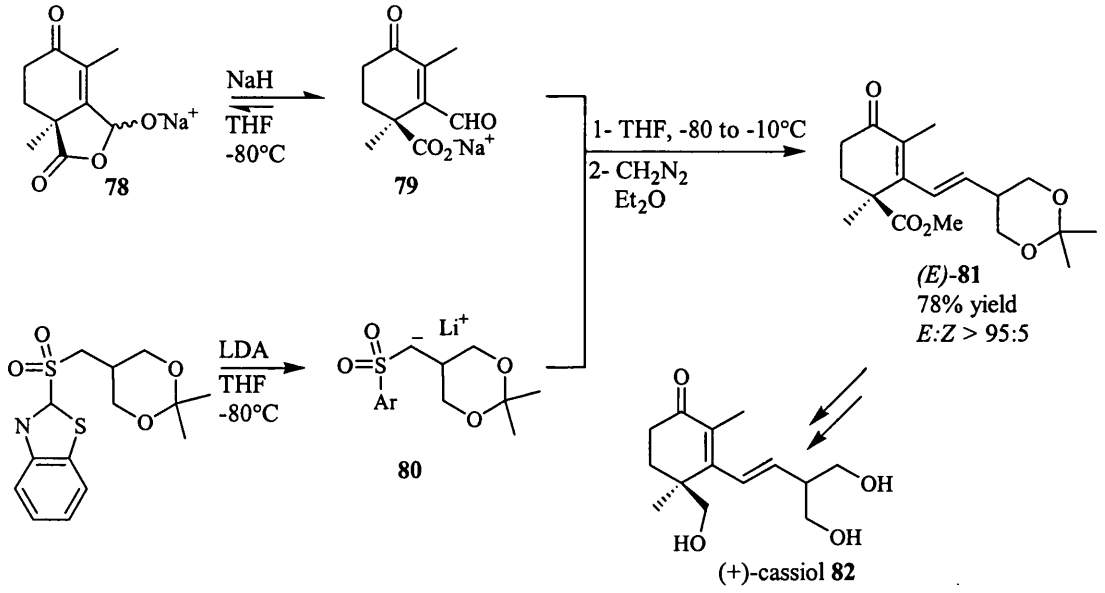
Danishefsky *et al.* have proposed a *novel* route to taxol **77** in which an epoxy group was used to protect an alkene at C11 of the taxane skeleton **75** which was reductively removed with SmI_2 to afford olefin *(E)*-**76** in excellent yield (Scheme 20).[31]



Scheme 20

2.1.10 The Julia olefination reaction

Ruveda *et al.* reported in 2003 a one-pot coupling reaction between lithiated benzothiazolylsulfone **80** and lactol alkoxide **78** (in equilibrium with carboxylate aldehyde **79**) to produce a synthon for the preparation of (+)-cassiol **82** as a single isomer (Scheme 21).[32]



Scheme 21

2.2 Stereoselective synthesis of trisubstituted electron-deficient alkenes

As described, a range of different procedures have been reported for the synthesis of α,β-unsaturated acid derivatives in a stereoselective fashion. Much of the research described in this thesis is directed towards the stereoselective synthesis of *(E)*-trisubstituted α,β-unsaturated amides, and as a consequence an in-depth review of the progress which has been made towards the stereoselective synthesis of trisubstituted acid derivatives is now described.

2.2.1 The Wittig reaction

The Wittig reaction has been the object of intense studies as a method of choice for the synthesis of trisubstituted α,β-unsaturated esters, amides and carboxylic acids in a stereoselective manner. As will be described, the vast majority of α,β-unsaturated acid derivatives prepared in this manner contain a methyl group at their α-position due to the prevalence of this structural motif in natural product targets arising from biosynthetic pathways.

2.2.1.1 The mechanism of the Wittig reaction

After more than 40 years the mechanism of the Wittig reaction is still under active investigation and initially will be discussed in general terms for the synthesis of disubstituted alkenes.[33,34] The reaction occurs *via* a three-step process, as drawn in Figure 11: first the phosphonium salt **83** is deprotonated α to the phosphorus atom to give stabilised ylid **84** that can also be considered as phosphorane **85**. This nucleophilic species then attacks the carbonyl group of the aldehyde **86**, generating reversibly the four-membered ring oxaphosphetane intermediates *syn*-**87** and *anti*-**90**, the ratio of which is highly dependent on the conditions of the reaction and the nature of the aldehyde employed as substrate. The oxaphosphetanes **87** and **90** then collapse *via* a final irreversible step to give alkenes *(Z)*-**88** and *(E)*-**91** with triphenylphosphine oxide as a by-product. The phosphorus-oxygen double bond is very strong (599.1 $kJ.mol^{-1}$),[35] and this factor is a major element in driving the reaction to completion.

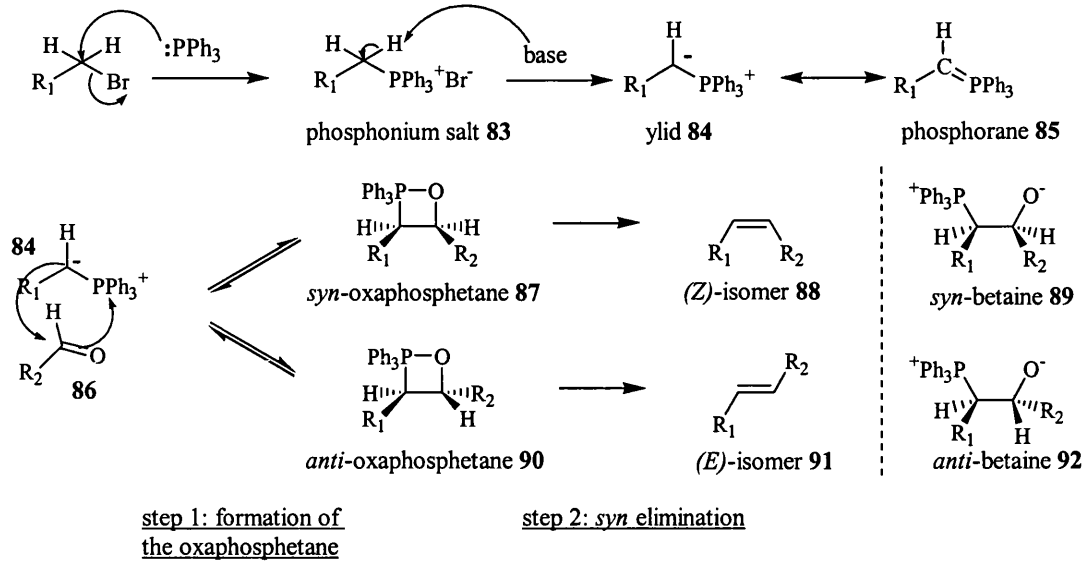


Figure 11

Oxaphosphetanes are very unstable species and for stabilised phosphoranes they have rarely been detected, even at temperatures as low as –80 to –100°C.[36] However the unusually stable oxaphosphetane **93** has been isolated and characterised by X-ray crystallography.[37] The resulting structure of oxaphosphetane **93**, as shown in Figure 12, revealed that phosphorus was at the centre of a distorted trigonal bipyramid with oxygen atoms occupying the apical positions.

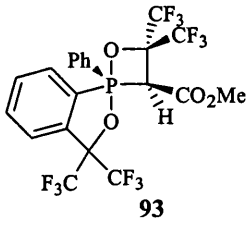
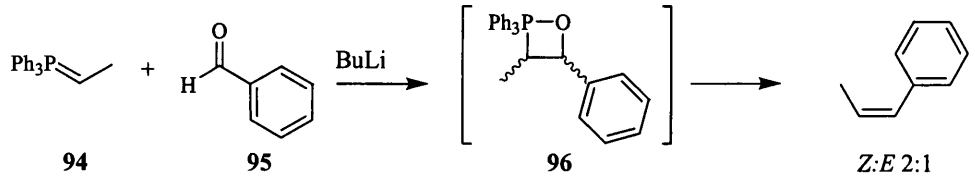


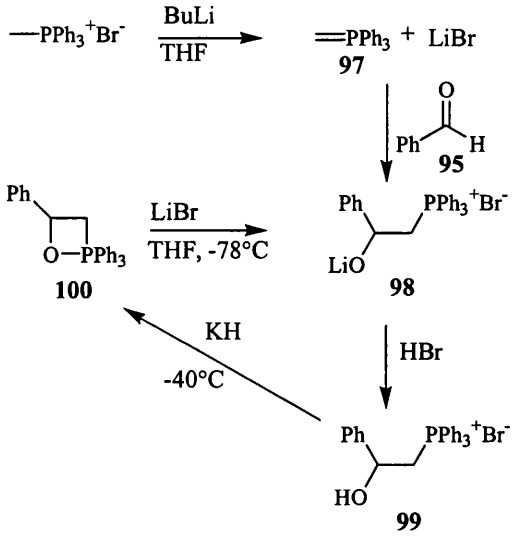
Figure 12

Vedejs *et al.* reported in 1973 the direct observation of oxaphosphetanes for the reaction between benzaldehyde **95** and an unstabilised phosphorane **94**.[38] The reaction was kept at –70°C and a sample was examined by ^{31}P NMR spectroscopy. The proton noise-decoupled spectrum at –70°C consisted of a broad singlet at δ 62.7 ppm (width of half-height, J = 15Hz), which was consistent with a pentavalent phosphorus species, such as oxaphosphetane **96** (Scheme 22).



Scheme 22

As a consequence oxaphosphetanes are currently favoured as true intermediates over another early contender, betaines **89** and **92** (Figure 11), which were considered for a few decades as intermediates in the Wittig reaction. Betaines have never been observed directly in any Wittig reaction under salt-free conditions, however they have been isolated in their complexed form with LiBr.[39] For example, Vedejs *et al.* isolated betaine **98** from the reaction of phosphorane **97** and benzaldehyde **95** in the presence of LiBr.[40] After dilute HBr workup, the hydroxyphosphonium salt **99** was isolated in good yield and reacted with KH at –40°C in THF to obtain pure oxaphosphetane **100**, since the ^{31}P NMR spectrum showed a broad resonance at δ –68 ppm characteristic of pentavalent phosphorus. Furthermore, addition of LiBr to a solution of oxaphosphetane **100** was shown to regenerate the betaine-lithium halide adducts **98** (Scheme 23). Therefore it appears that betaines may not be true precursors of oxaphosphetanes, but instead reversible by-products of the reaction of intermediate oxaphosphetanes and lithium salts generated *in situ*.[41]



Scheme 23

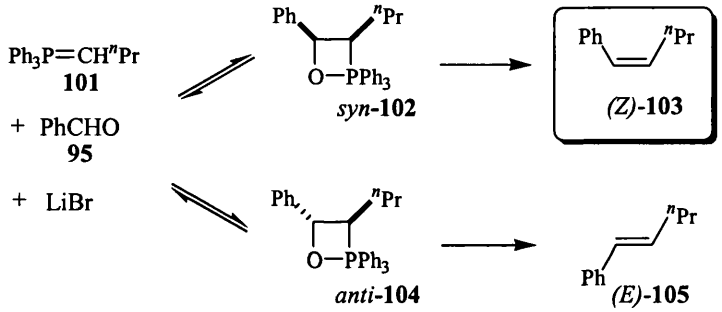
Finally, Eisenstein *et al.* demonstrated, with the help of *ab initio* calculations under salt free conditions,[42] that oxaphosphetanes are likely to be favoured over betaines as intermediates in the Wittig reaction. It is noteworthy that several mechanistic and kinetic studies have been conducted which led to the proposal of other potential mechanisms that are less widely accepted.[43,44]

2.2.1.2 Stereoselectivity considerations

The oxaphosphetane is a short-lived intermediate which even at low temperature collapses to an alkene product *via* a *syn*-elimination pathway. Therefore, the stereochemical outcome

of the Wittig reaction is determined in the oxaphosphetane-forming step, as well as by the degree of reversibility of this reaction to afford starting materials.

Maryanoff *et al.* have reported the rate study on the reaction of non-stabilised phosphorane **101** and benzaldehyde **95** in THF at –30°C in the presence of LiBr.[45,46] The relative ratio of *cis*- and *trans*-oxaphosphetanes **102** and **104** formed was measured over 5 hours, the initial ratio was established to be 78:22, and compared to the final *Z:E* alkene ratio **103**:**105**, 55:45 (Scheme 24). Maryanoff described this discrepancy as stereochemical drift and proposed it as a measure of the reversibility of the reaction. The salt-free reaction of phosphorane **101** and benzaldehyde **95** was monitored using the same procedure. The relative ratio of *syn*- and *anti*-oxaphosphetanes **102** and **104** remained constant throughout the reaction, affording a final *Z:E* ratio **103**:**105** of > 95:5. Therefore the formation of oxaphosphetanes from an unstabilised ylid under salt-free conditions appears to be essentially irreversible. The major intermediate is then the *syn*-oxaphosphetane and the reaction is said to be kinetically controlled, and will afford a *(Z)*-alkene (Scheme 24).



Scheme 24

The question arises as to why the *syn*-oxaphosphetane **87** is formed as the kinetic product in preference to the *anti*-oxaphosphetane **90**. Conventional wisdom states that reaction of the phosphorane **85** and the aldehyde **86** occurs to afford a *syn*-oxaphosphetane **87** because this trajectory of attack minimises steric interactions between R_1 of the phosphorane **85** and R_2 of the aldehyde **86**. In contrast the transition state leading to the *anti*-oxaphosphetane **90** requires that the R_1 group of the phosphorane **85** and the R_2 substituent of the aldehyde **86** are orientated in close proximity to each other, a situation which is clearly disfavoured relative to the *syn*-oxaphosphetane **87** transition state (Figure 13).

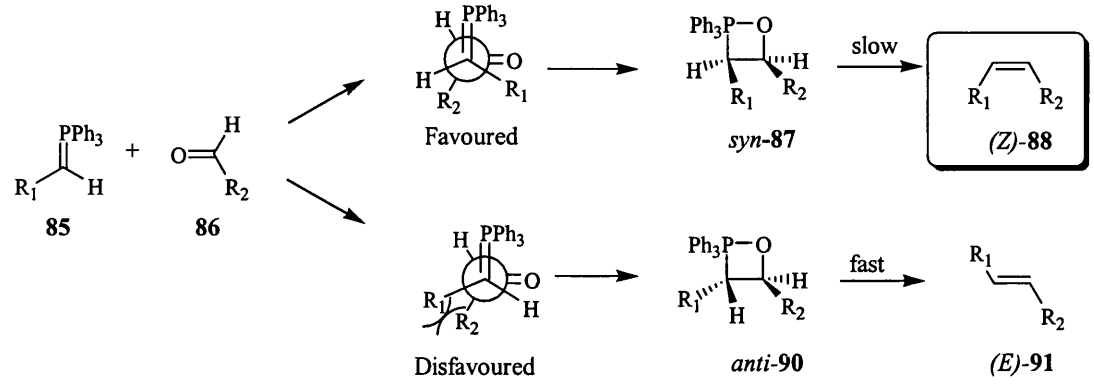


Figure 13

Unlike unstabilised ylids, the reaction of EWG-stabilised phosphorane **107** with aldehyde **106** affords the *(E)*-isomer **109** as the major diastereomer. The dominant explanation to account for this reversal in stereoselectivity is the potential reversibility in the formation of the oxaphosphetane intermediate.[47] Clearly reversibility of this initial step facilitates equilibration of the *anti-* and *syn*-oxaphosphetane **108** and **110** intermediates, at a faster rate than their corresponding elimination to afford *(E)-* and *(Z)*-alkenes **109** and **111** respectively. This would ensure that the thermodynamically more stable *anti*-oxaphosphetane intermediate **108** predominates, and consequently the *(E)*-alkene **109** is formed as the major product (Figure 14).

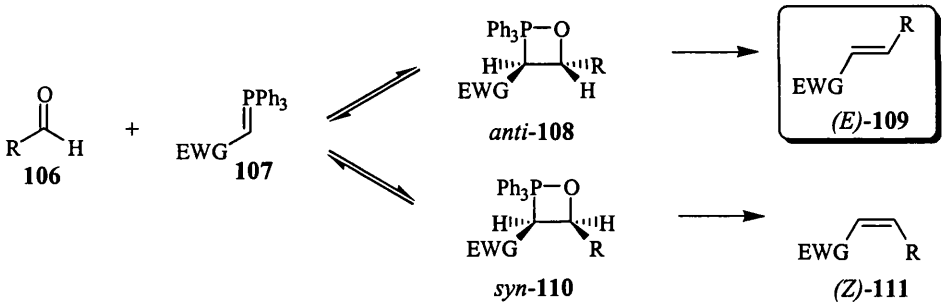
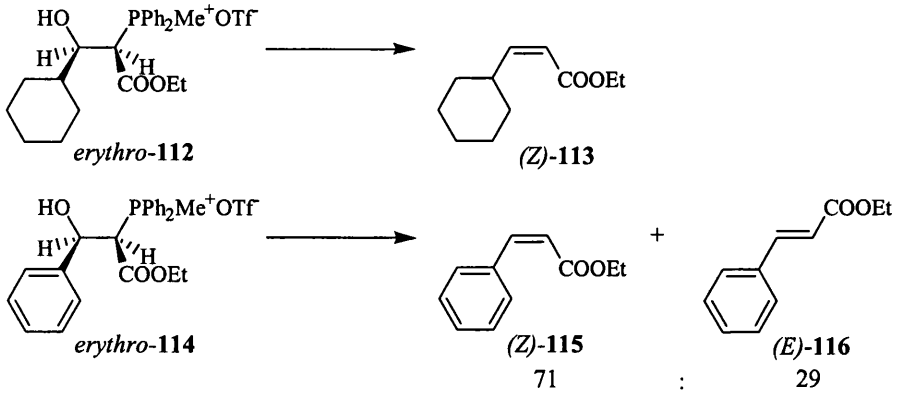


Figure 14

However, Vedejs *et al.* have questioned this assumed reversibility in the formation of these type of oxaphosphetane intermediates.[48] He has reported on deprotonation studies of stabilised β-hydroxy phosphonium salts where for the case of an aliphatic aldehyde the erythro salt **112** was shown to produce a *(Z)*-alkene **113** stereoselectively, thus implying the absence of any reversibility in the *(E)*-selective addition of a stabilised ylid to an aliphatic aldehyde. In the case of β-hydroxyphosphonium salt **114** derived from an aromatic aldehyde some degree of reversibility in the formation of oxaphosphetane intermediate was observed, affording a significant amount of ester *(E)*-**116** under thermodynamic control (Scheme 25).[36]

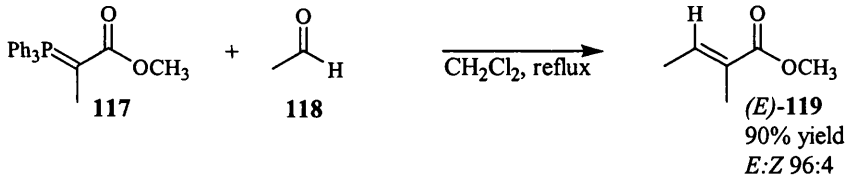


Scheme 25

2.2.1.3 The Wittig reaction of stabilised phosphoranes is *(E)*-selective

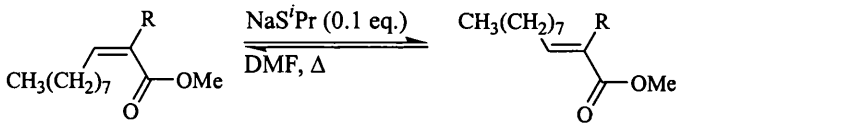
As we have seen the Wittig reaction of stabilised phosphoranes for the synthesis of disubstituted alkenes is *(E)*-selective and has proven very popular in research groups in both industry and academia due to its ease of application and its versatility, particularly for the synthesis of natural products.

In a landmark publication in 1961, House *et al.* reported that reaction of α-methyl-phosphorane **117** and acetaldehyde **118** gave methyl *(E)*-2-methyl-2-butenoate **119** in 92% d.e. (Scheme 26).[47]



Scheme 26

Clearly from the discussion in the previous section this class of trisubstituted *(E)*-unsaturated ester is likely to be formed under thermodynamic control, due to the stabilising effect of the ester group. At first sight it is unclear if an *(E)*-ester of this type is more thermodynamically stable than its *(Z)*-isomer, however work by Marshall *et al.* has demonstrated this to be the case.[49] They reported that treatment of *(Z)*-trisubstituted-α,β-unsaturated methyl ester **120** with sodium isopropylthiolate in DMF at high temperatures under equilibrating conditions afforded *(E)*-conjugated ester **122** as the major product. Likewise a 60:40 mixture of *(E)*- and *(Z)*-conjugated esters **120** and **122** under those conditions gave the same *(E)*-isomer **122** in a *E:Z* ratio of 93:7. Longer alkyl chains at the α-position (entries 3, 4) did shift the equilibrium, although the *(E)*-isomer **123** was still more stable than the *(Z)*-isomer **121** (Scheme 27, Table 1).



(Z)-**120**
(Z)-**121**

(E)-**122**: R = CH_3
(E)-**123**: R = $(CH_2)_9CH=CH_2$

Scheme 27

				E:Z	
	R_1	**Time (hrs)**	**T (°C)**	**initial**	**final**
1	CH_3	0.5	90	4 / 96	90 / 10
2	CH_3	16	140	60 / 40	93 / 7
3	$(CH_2)_9CH=CH_2$	18	140	7/ 93	63 / 37
4	$(CH_2)_9CH=CH_2$	15	140	99 / 1	93 / 7

Table 1

It appears therefore that the ester functionality in the reaction of α-substituted stabilised Wittig reagent **117** must be more sterically demanding than the α-methyl substituent such that formation of *anti*-oxaphosphetane **125** is favoured over formation of *syn*-oxaphosphetane **126** under thermodynamic control (Figure 15).

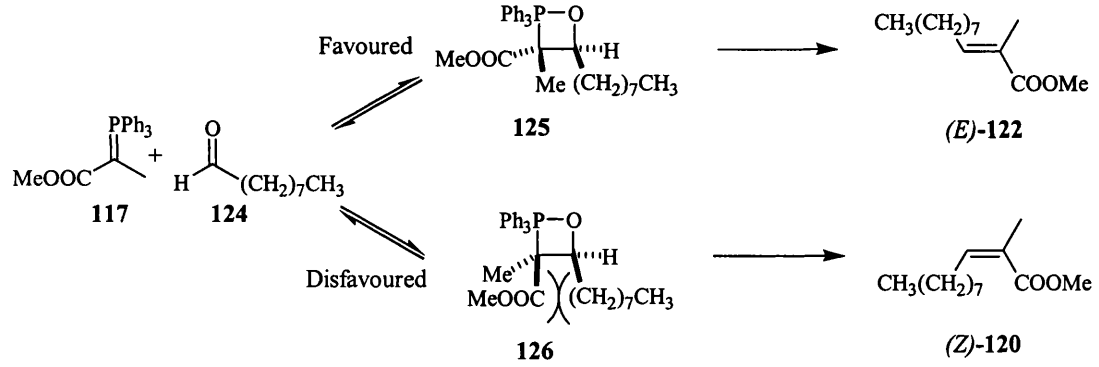
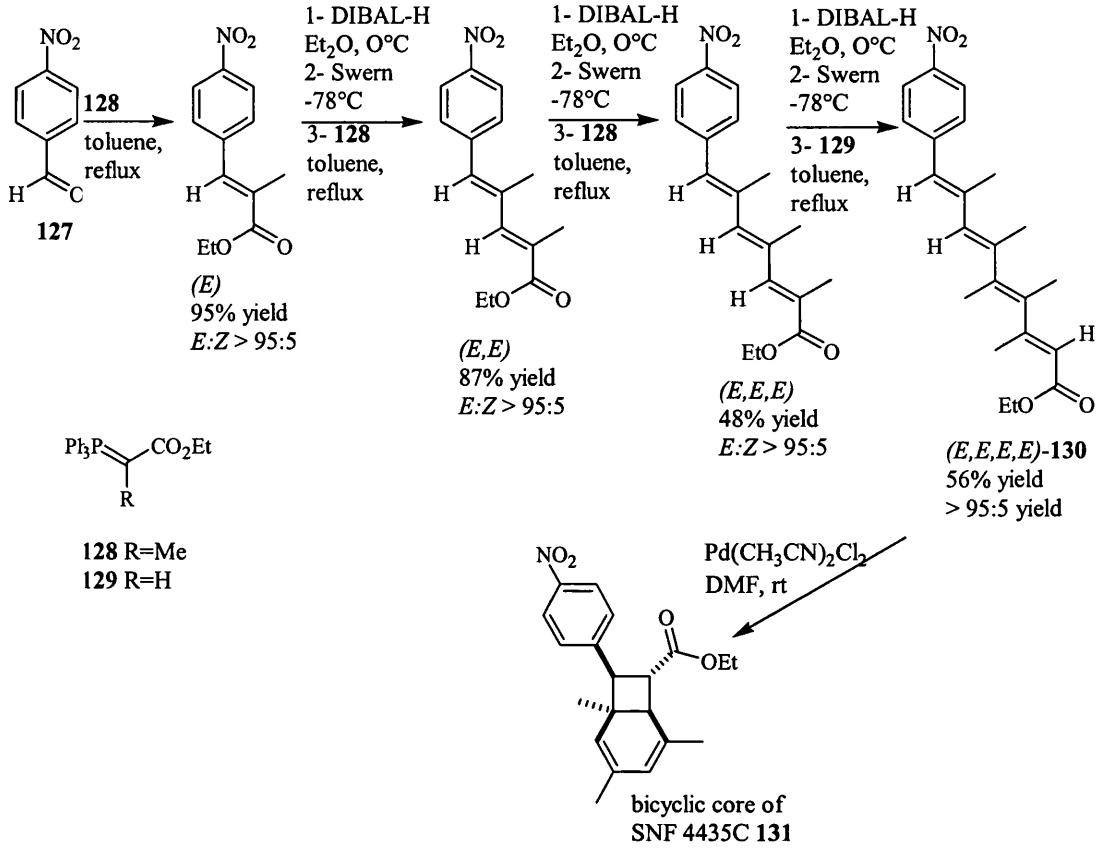


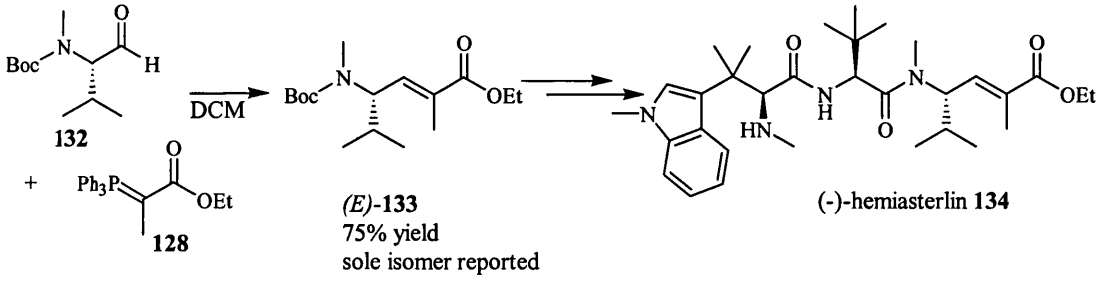
Figure 15

The use of α-methyl stabilised Wittig reagents for the formation of trisubstituted *(E)*-α,β-unsaturated esters has been widely used in natural product synthesis. Its predictability has recently been elegantly demonstrated by Baldwin *et al.* who reported the iterative Wittig reaction of *p*-nitrobenzaldehyde **127** with phosphoranes **128** and **129** to access the sterically crowded *(E,E,E,E)*-tetraene **130**, which was employed as a substrate for electrocyclic ring closure to afford the bicyclic core **131** of the *novel* immunosuppressant SNF 4435C (Scheme 28).[50]



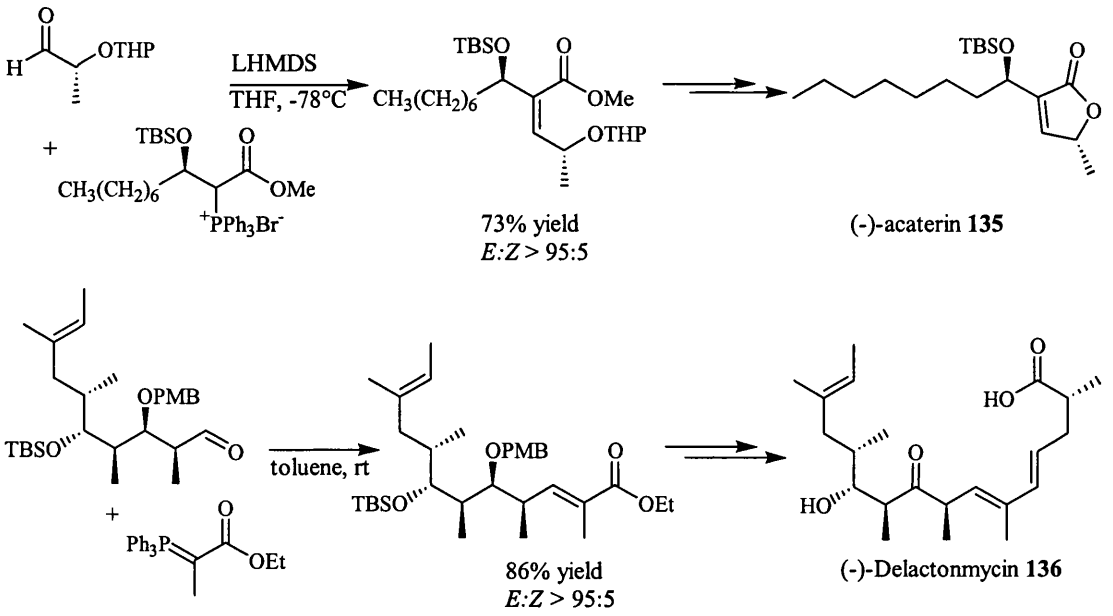
Scheme 28

Andersen *et al.* have reported the total synthesis of (-)-hemiasterlin **134**, a structurally *novel* tripeptide that exhibits potent cytotoxic activity, involving reaction of aldehyde **132** with stabilised phosphorane **128** to afford *(E)*-α,β-unsaturated ethyl ester **133** as the only isomer in a highly stereoselective manner and with complete retention of the integrity of the stereogenic centre (Scheme 29).[51]



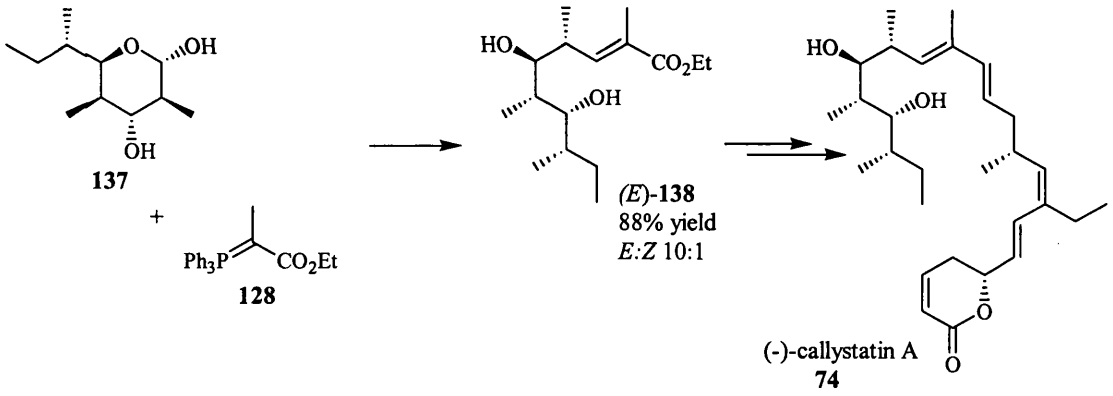
Scheme 29

A range of other groups have also used the Wittig reaction in their routes to complex natural products, such as (-)-acaterin **135** and (-)-delactonmycin **136** observing excellent diastereoselectivities, and no racemisation of neighbouring stereogenic centres (Scheme 30).[52,53]



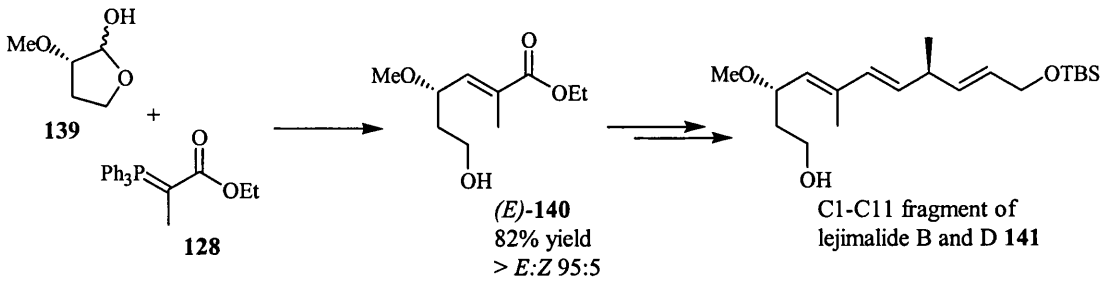
Scheme 30

Amos Smith III *et al.* undertook the total synthesis of the highly popular synthetic target (-)-callystatin A **74**. Latent aldehyde equivalent **137** was reacted with stabilised phosphorane **128** to afford α,β-unsaturated ethyl ester **138** with retention of configuration of all the stereogenic centres (Scheme 31). The major *(E)*-isomer **138** was purified *via* conversion to its corresponding lactone.[54]



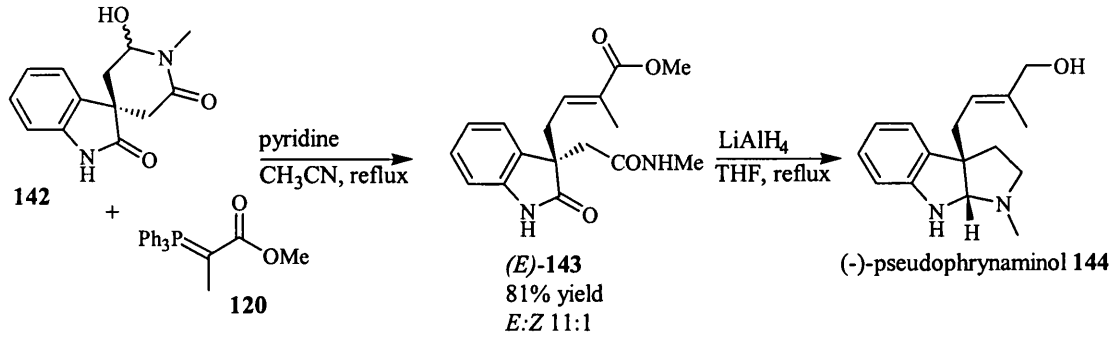
Scheme 31

This type of Wittig reaction has also been reported for other masked aldehyde substrates. Rein, Helquist *et al.* have reported the stereocontrolled synthesis of the C1-C11 fragment **141** of Iejimalide B and D which exhibits potent *in vitro* antitumor activity. Thus, the reaction of hemiacetal **139** and phosphorane **128** afforded α,β-unsaturated ester **140** in good yield and as the sole isomer (Scheme 32).[55]



Scheme 32

On their route towards the stereoselective synthesis of alkaloid (-)-pseudophrynaminol **144**, Kawasaki *et al.* employed aminal **142** and α-substituted phosphorane **120** in a Wittig reaction to afford α,β-unsaturated ester **143** in good yield and selectivity (Scheme 33).[56]



Scheme 33

2.2.2 The Horner-Wadsworth-Emmons (HWE) reaction

Due to difficulties arising from separation of reaction side-products (triphenylphosphine oxide) of the Wittig reactions and the general lack of reactivity of some stabilised ylides substituted with an electron-withdrawing group, another popular method of alkene formation is sometimes favoured: the HWE modification. This approach involves the use of phosphonate esters (or the corresponding nitriles or ketones) that can be deprotonated with sodium hydride or alkoxide anions to give enolate-type anions, which react well with aldehydes or ketones to give *(E)*-alkenes, and under certain specific conditions *(Z)*-alkenes.

2.2.2.1 The mechanism of the HWE reaction

Phosphonate anions are strongly nucleophilic and react readily with carbonyl compounds under mild conditions to form olefins and water-soluble phosphate esters. In the case of phosphonate esters the anions are doubly stabilised by the presence of the carbonyl group and the phosphonate group. It is widely accepted that the HWE reaction once again occurs under thermodynamic control to afford predominantly *(E)*-olefins *via* a mechanism similar to that of the Wittig reaction (Figure 16).[57] Thus the stabilised phosphonoester **145** attacks

the carbonyl of the aldehyde **146** and reversibly forms *syn*- and *anti*-oxaphosphetane **147** and **149** where the stereochemistry of the alkene is determined by the stereoselectivity in the initial carbon-carbon bond-forming step.[58] Once again, the *anti*-oxaphosphetane **147** is generally considered to be more stable than the corresponding *syn*-oxaphosphetane **149** and collapses irreversibly to the *(E)*-isomer **148**.

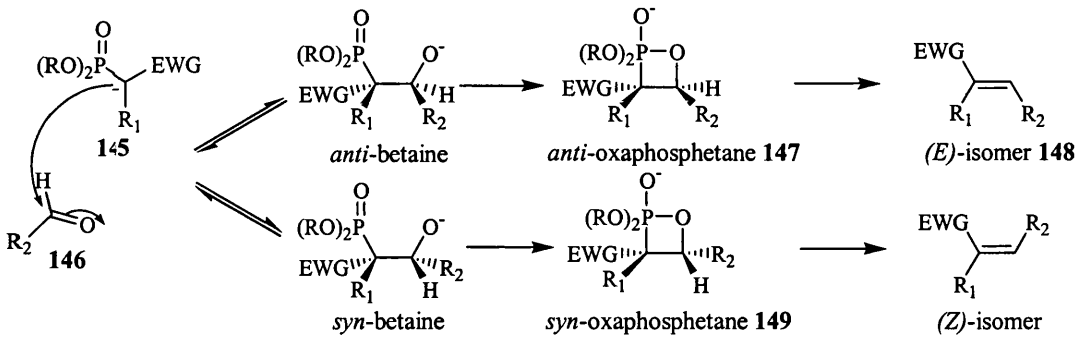
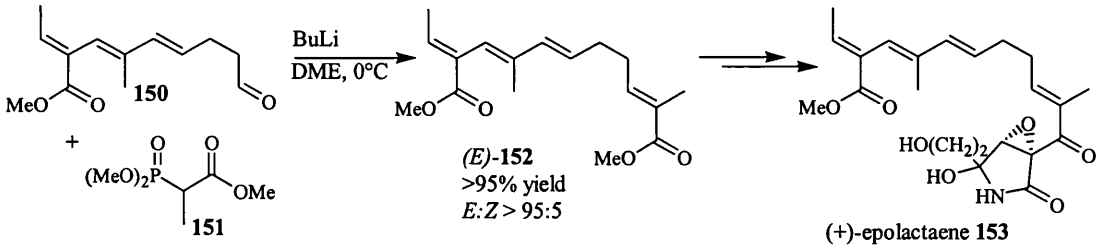


Figure 16

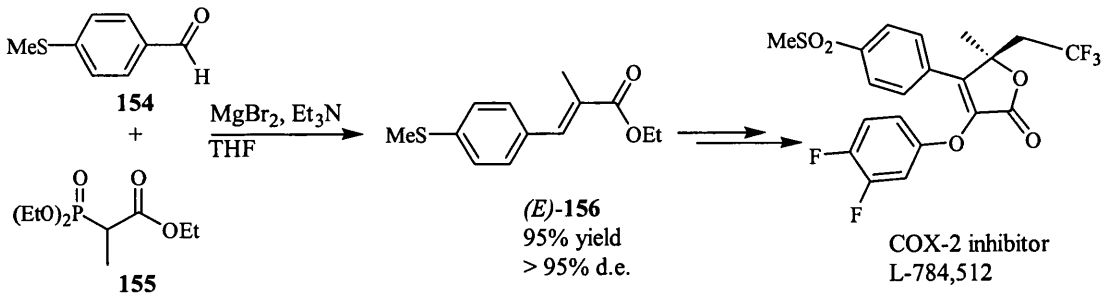
2.2.2.2 The HWE reaction of stabilised phosphonates is *(E)*-selective

Hayashi *et al.* have employed the HWE reaction in their total synthesis of epolactaene **153**. α-Methyl-phosphonate ester **151** reacted with triene aldehyde **150** in a stereoselective manner to afford *(E)*-α,β-unsaturated ester **152** as essentially the only stereoisomer formed in quantitative yield (Scheme 34).[59]



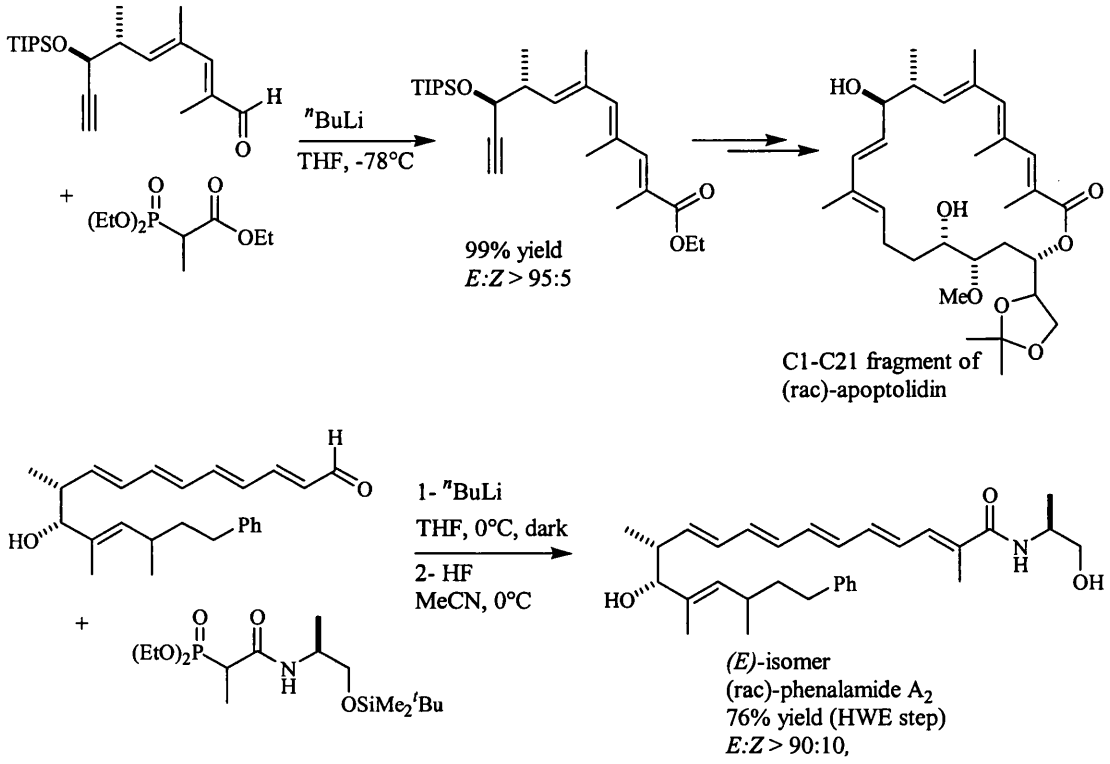
Scheme 34

Tan *et al.* have reported the facile condensation of *p*-methylthiobenzaldehyde **154** with phosphonate **155** to afford *(E)*-trisubstituted ethyl ester **156** quantitatively, once again as the sole isomer (Scheme 35).[60]



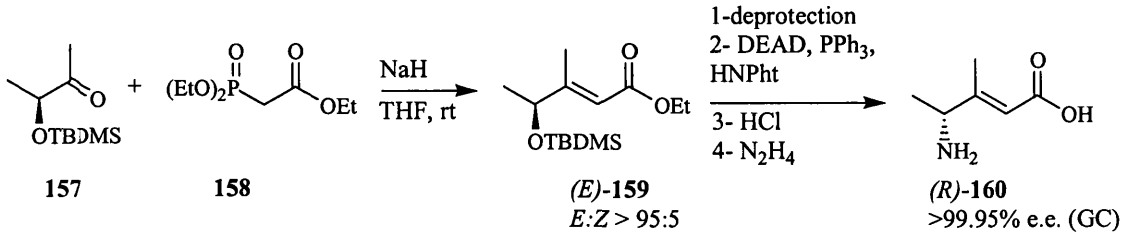
Scheme 35

This theme is a general one, since many different groups in recent years have used the HWE reaction as a stereoselective tool to introduce efficiently unsaturated esters and amides into synthons for natural product synthesis, and a representative range of examples are described in Scheme 36.[61,62]



Scheme 36

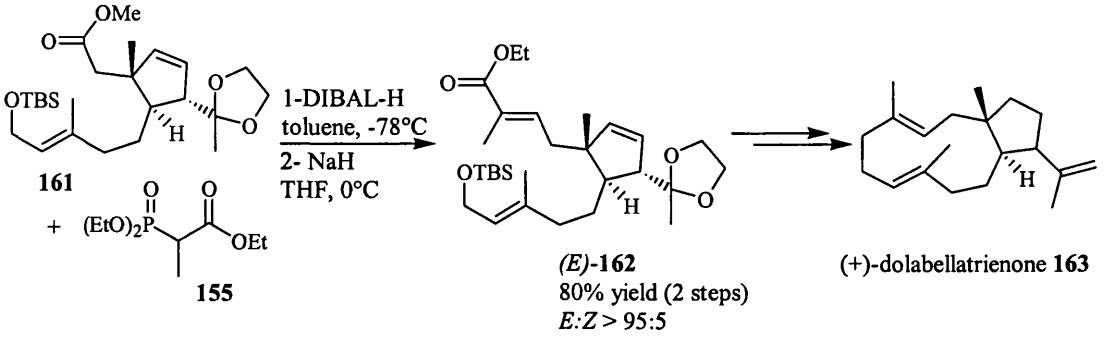
Mulzer *et al.* reported in 1995 a synthesis of α,β-unsaturated γ-amino acid *(R)*-**160** with excellent enantioselectivity.[63] Attack of the phosphonate **158** onto electrophilic ketone **157** afforded *(E)*-α,β-unsaturated ester **159** without racemisation of the stereogenic centre in the γ position. Deprotection of the silylether **159**, followed by inversion of the stereocentre using the aza-Mitsonobu reaction led to the α,β-unsaturated γ-amino acid **160** (Scheme 37).



157 **158** *(E)*-**159** *E:Z* > 95:5 *(R)*-**160** >99.95% e.e. (GC)

Scheme 37

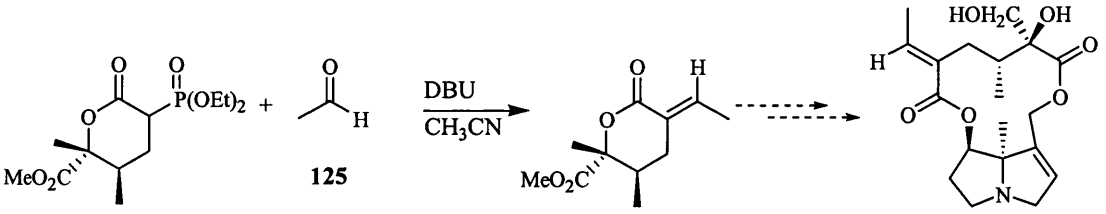
Yamada *et al.* reported an enantioselective route of (+)-dolabellatrienone **163** where they employed the HWE reaction for the synthesis of a late stage intermediate.[64] Thus, reduction of ester **161** with DIBAL-H and reaction with phosphonate **155** in the presence of NaH afforded *(E)*-α,β-unsaturated amide **162** in a highly diastereoselective fashion (Scheme 38).



161 + **155** *(E)*-**162** 80% yield (2 steps) *E:Z* > 95:5 (+)-dolabellatrienone **163**

Scheme 38

Finally, Wiemer *et al.* has reported on the HWE condensation of α-phosphonolactone **164** and acetaldehyde **125** to afford with modest stereoselectivity highly functionalised intergerrinecic acid lactone **165**, which was used as an intermediate for the synthesis of usaramin **166** (Scheme 39).[65]



164 **125** *(E)*-**165** 77% yield *E:Z* 9:1 usaramin **166**

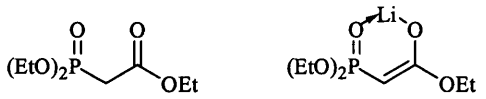
Scheme 39

2.2.2.3 The modified HWE reaction in the presence of metal salts

So far we have described the successful preparation of *(E)*-α,β-unsaturated esters *via* HWE reaction, where the generation of the phosphonate carbanion is achieved using a relatively strong base such as ^{n}butyllithium, potassium ^{t}butoxide, or sodium hydride. Under certain

circumstances the aldehyde component may be sensitive to strong bases, and competing racemisation, aldol condensation, or decomposition of the aldehyde can occur, and thus milder conditions are preferable.

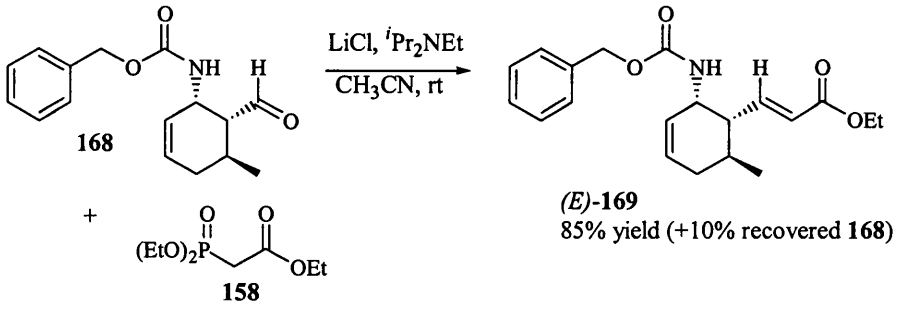
Seyden-Penne *et al.* described the formation of a tight complex **167** between a lithium cation and the carbanion derived from phosphonate **158** (Figure 17) and showed that in the presence of a lithium salt that phosphonates could be deprotonated with milder bases such as a tertiary amine.[66]



158 **167**

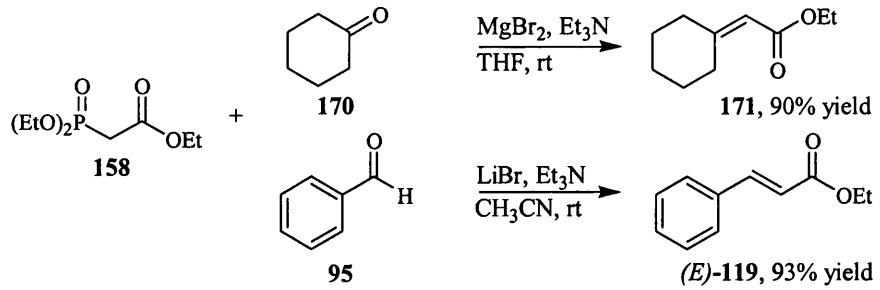
Figure 17

For example, in 1984, Masamune, Roush *et al.* reported that phosphonate **158**, complexed with lithium cation could be deprotonated with mild base such as DBU or diisopropylethylamine to generate a reactive phosphonate carbanion.[67] Addition of aldehyde **168** gave *(E)*-disubstituted α,β-unsaturated ester **169**, thus avoiding epimerisation of the stereogenic centre, which had been previously reported for the same system in the presence of sodium hydride (Scheme 40).



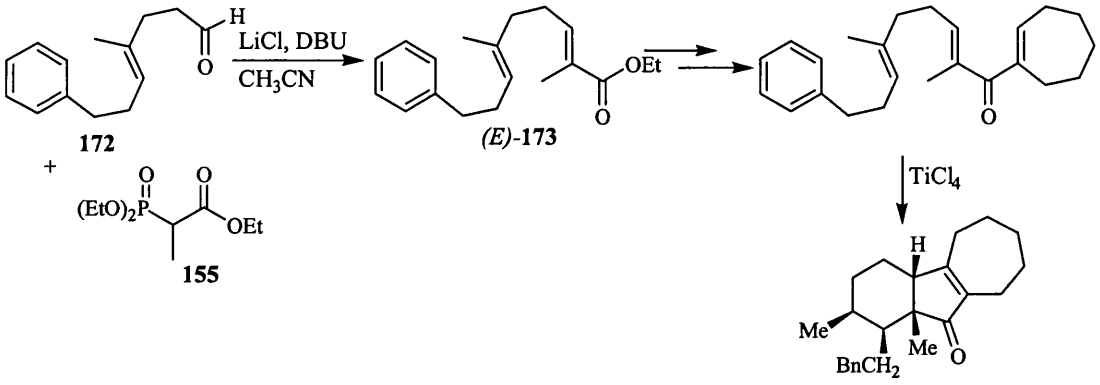
Scheme 40

In parallel studies to this work Rathke *et al.* reported that lithium or magnesium salts also facilitate the use of a weak base such as triethylamine, thereby extending the range of conditions introduced by Masamune, Roush *et al.* Thus, reaction of cyclohexanone **170**, and benzaldehyde **95** with phosphonate **158** afforded the olefinated substrates *(E)*-**171** and *(E)*-**119** in a stereoselective fashion (Scheme 41).[68]



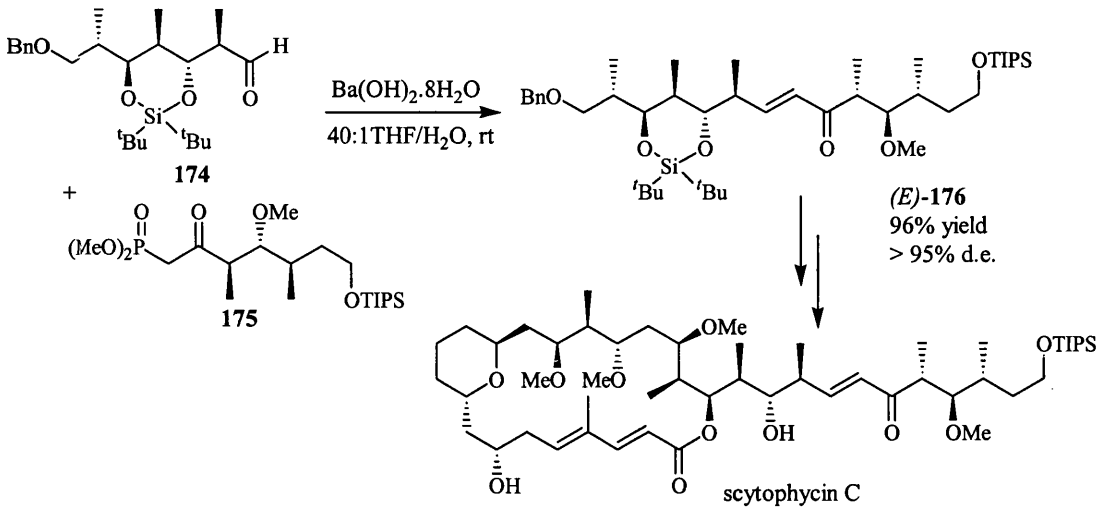
Scheme 41

In 1999 West *et al.* reported the preparation of ethyl ester *(E)*-**173** from methyl substituted phosphonate **155** in good yield and selectivity using the conditions developed by Masamune, Roush *et al.* (Scheme 42). Importantly no products arising from aldol condensation of aldehyde **172** with itself were observed.[69]



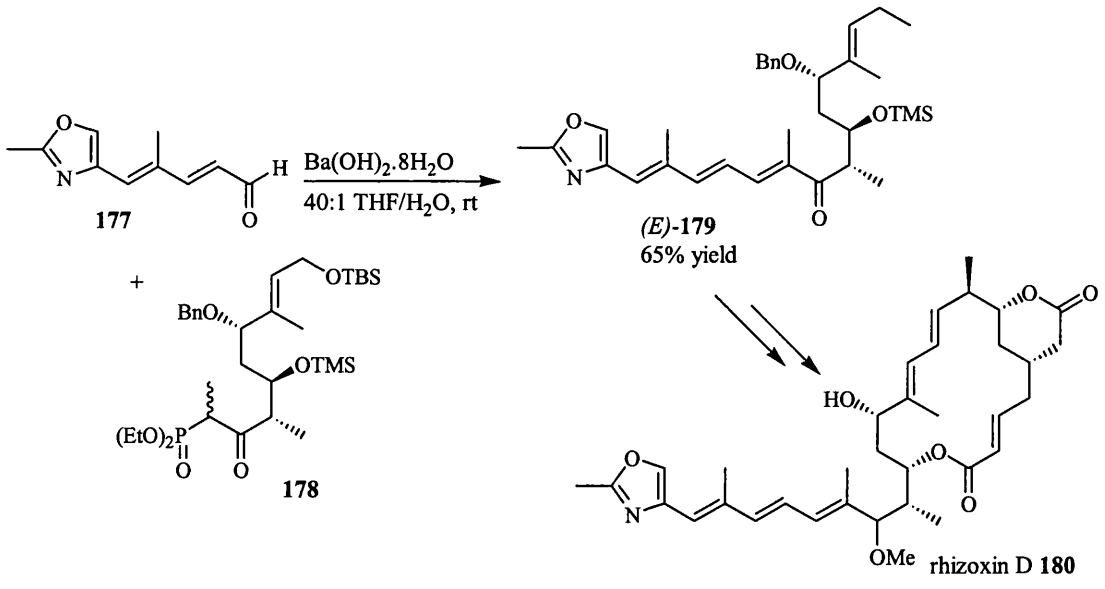
Scheme 42

Paterson *et al.* have found that reaction of β-ketophosphonate **175** and labile aldehyde **174** under strongly basic conditions led to the epimerisation of the final product at the α-position. However the milder protocol proposed by Masamune, Roush *et al.* was found to give a poor conversion to the final product *(E)*-**176**. Consequently he demonstrated that barium hydroxide was effective in this system for a range of functionalised β-ketophosphonates.[70] Thus the reaction of phosphonate **175** and labile aldehyde **174** with barium hydroxide afforded α,β-unsaturated ketone *(E)*-**176** in 96% yield and > 95% d.e. (Scheme 43).



Scheme 43

This novel procedure has found further application in the synthesis of natural product synthesis using α-substituted phosphonates. For example, Leahy *et al.* reported in 2003 an enantioselective synthesis of the popular target antitumor macrolide rhizoxin D.[71] The olefination reaction involving oxazole-based aldehyde **177** and highly functionalised β-ketophosphonate **178** failed under the conditions proposed by Masamune and Roush. However the modification introduced by Paterson *et al.* proved to be highly successful in affording *(E)*-trisubstituted-α,β-unsaturated ketone **179** in 65% yield and as the only isomer (Scheme 44).

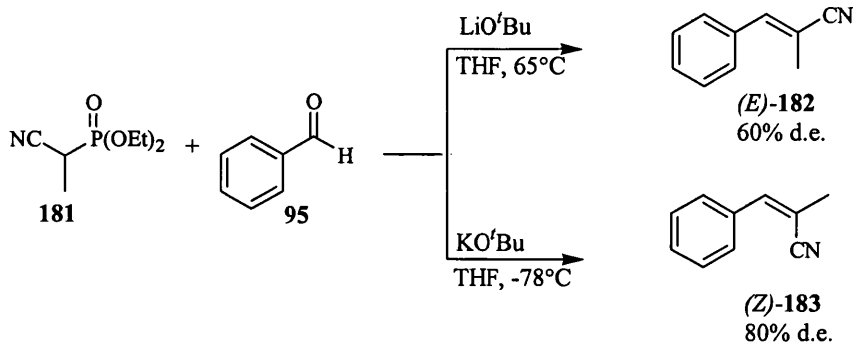


Scheme 44

2.2.2.4 Progress towards the development of a *(Z)*-selective HWE reaction

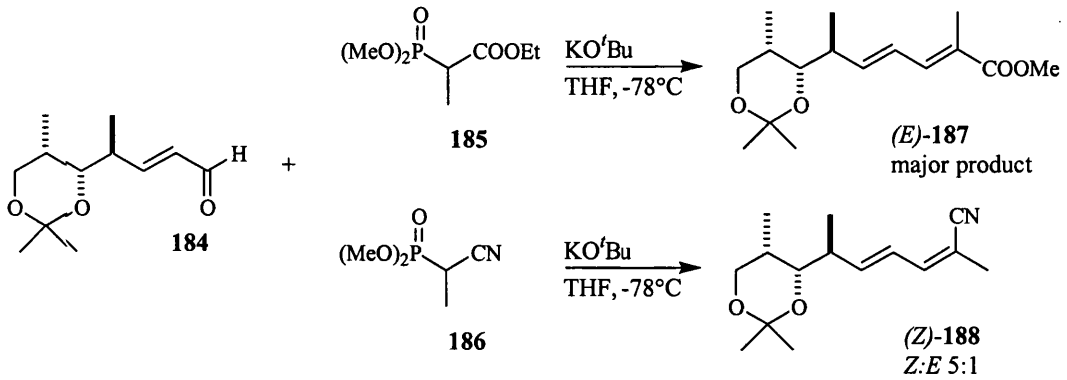
As we have seen reaction of aldehydes with stabilised ylides such as **155** occurs with *(E)*-selectivity. However, it has been found that *(Z)*-selectivity may be obtained under certain conditions where formation of oxaphosphetanes and irreversible elimination to olefin products is quicker than their equilibration with starting materials.

In 1974 Seyden-Penne *et al.* reported on the influence of the counter *cation* and temperature in the reaction between stabilised phosphonitrile **181** and benzaldehyde **95** (Scheme 45).[72] The use of ^{t}BuOLi in the HWE reaction of ylide **181** and benzaldehyde **95** at +65°C afforded the thermodynamic product *(E)*-**182** with 60% d.e.; whilst the same reaction using ^{t}BuOK as a base at –78°C gave the *(Z)*-olefin **183** with 80% d.e., indicating that no equilibration was occurring at low temperature, and that *(Z)*-**183** was being formed under kinetic control.



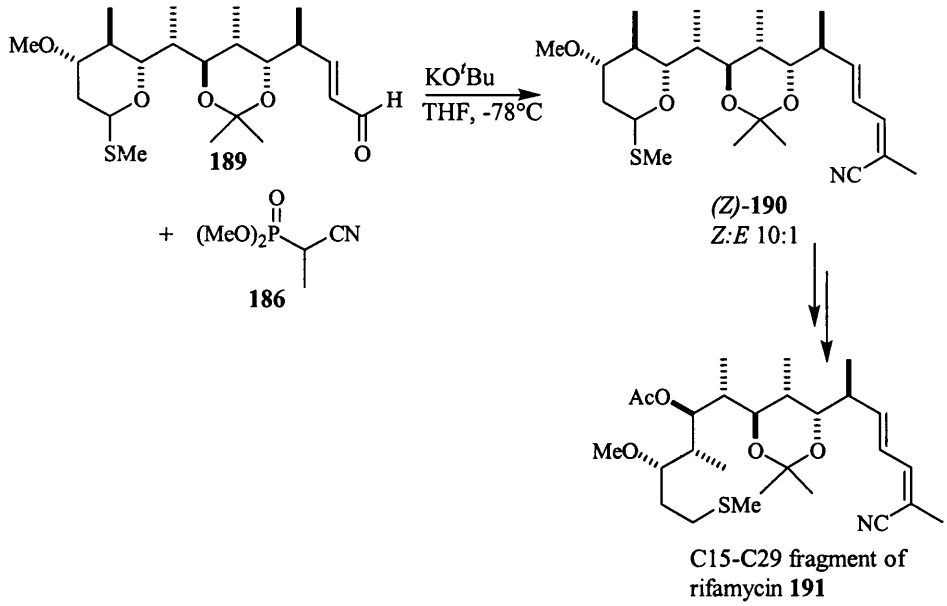
Scheme 45

In the HWE reaction, phosphonitriles were found to be even more sensitive to changes in metal cation and temperature. Kishi *et al.* reported in 1980 that whilst ester-stabilised phosphonate **185** reacted with aldehyde **184** to afford *(E)*-isomer **187** as the major product, the corresponding cyano conjugated phosphonate **186** gave the alternative *(Z)*-stereoisomer **188** under the same conditions (Scheme 46).[73]



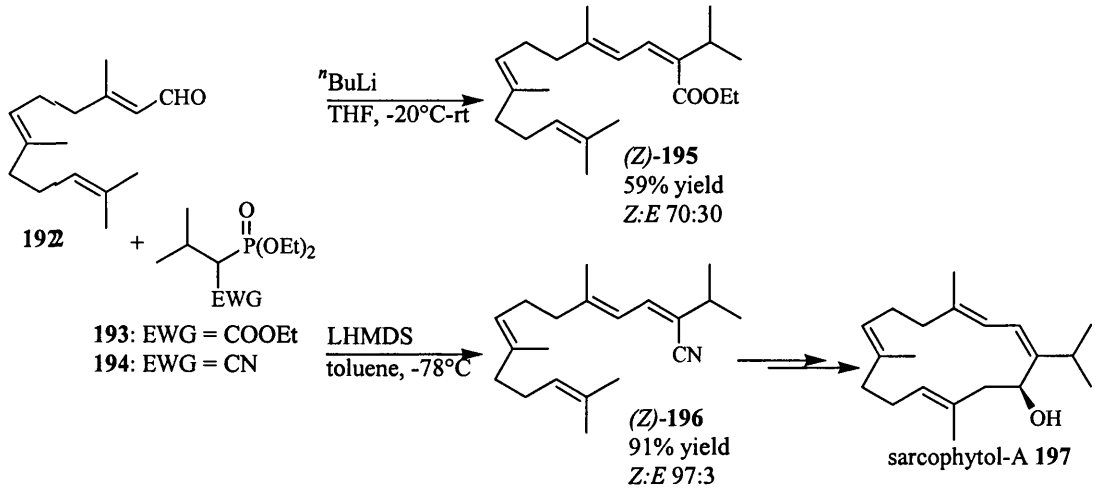
Scheme 46

It is noteworthy that when this *novel* procedure was applied to the preparation of the related *(Z)*-α,β,γ,δ-*bis*-unsaturated cyanide **190** *via* reaction of aldehyde **189** with nitrile **186** the *(Z)*-stereoselectivity was 10:1 enabling a protected C15-C29 fragment **191** of rifamycin to be prepared (Scheme 47).



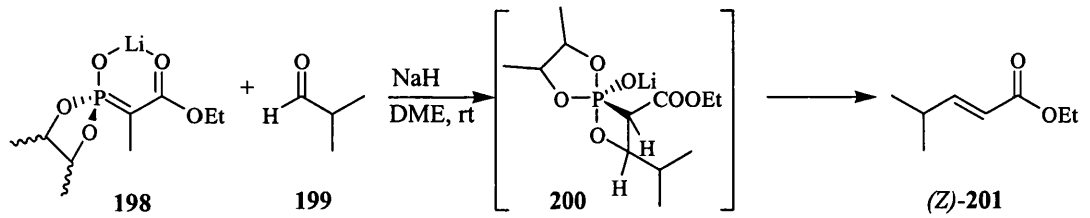
Scheme 47

Similarly, while designing an enantioselective route to naturally-occurring cancer chemopreventive agent sarcophytol A **197**, Takayanagi *et al.* have reported that the Horner-Emmons reaction at -20°C between phosphonate ethyl ester **193** and aldehyde **192** afforded *(2Z,4E)*-diene **195** in 40% d.e.[74] Although decreasing the reaction temperature tended to increase the *(Z)*-selectivity, the HWE reaction was found not to occur below –20°C. However the Horner-Emmons reaction of phosphonate nitrile **194** at –78°C produced *(2Z,4E)*-diene **196** in 94% d.e. (Scheme 48)



Scheme 48

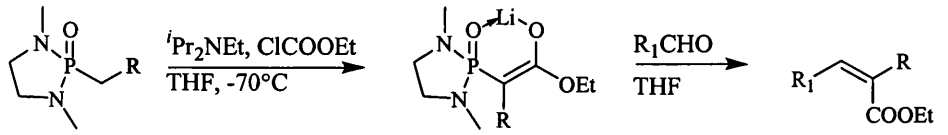
In 1977 Breuer *et al.* and Seyden-Penne *et al.* proposed that the enolate **198** of a cyclic phosphonate in which the phosphorus atom was constrained within a five-membered ring would be forced to adopt a strained tetrahedral geometry.[75,76] They reasoned that this strain would be released on reaction with an aldehyde, such as isobutyraldehyde **199**, to form oxaphosphetane **200** where the phosphorus atom would now adopt a less strained trigonal bipyramidal geometry. Oxaphosphetane would then decompose rapidly under kinetic control to afford the *(Z)*-isomer **201** as the major product (Scheme 49).



198 **199** **200** ***(Z)*-201**
Z:E 68:32

Scheme 49

In 1991 Savignac *et al.* screened some oxygen and nitrogen-containing ring systems, and demonstrated that spirophosphoranes **202** reacted with a range of aliphatic aldehydes to afford *(Z)*-trisubstituted α,β-unsaturated ethyl ester **203** (Scheme 50).[77]

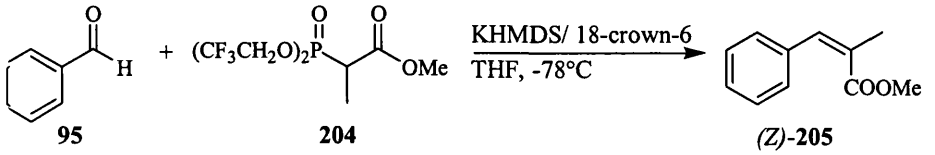


202

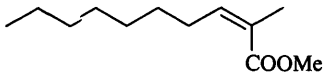
***(Z)*-203**
R= H, Me, Et, ^{n}Pr
R_1= Me, ^{n}Pr, ^{i}Pr, ^{i}Bu
>65% yield
64-94% d.e.

Scheme 50

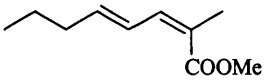
In 1983 Still *et al.* reported that the HWE reaction of electrophilic trifluoroethyl phosphonate **204** and benzaldehyde **95** produced *(Z)*-α,β-unsaturated methyl ester **205** in 66% d.e.[78] They also reported that employing strongly dissociated base systems like KHMDS/18-crown-6 allowed the *(Z)*-selectivity to reach > 96% d.e. Under those optimised conditions, aromatic, saturated and unsaturated aliphatic aldehydes reacted successfully with phosphonate **204** to afford *(Z)*-esters **206a-c** in a highly stereoselective fashion (Scheme 51).



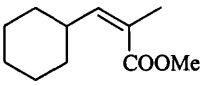
95 **204** ***(Z)*-205**
94% d.e.
>95% yield



***(Z)*-206a**
96% d.e.
88% yield



***(Z)*-206b**
>96% d.e.
79% yield

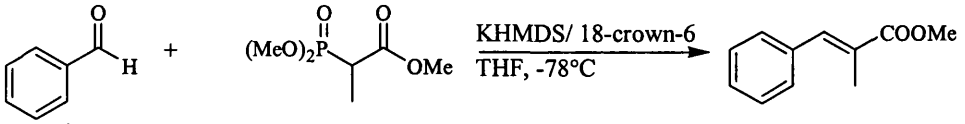


***(Z)*-206c**
>96% d.e.
80% yield

Scheme 51

As has been described, the HWE reaction is generally believed to proceed under thermodynamic control (see section 2.2.2.1). However the electron-withdrawing capacity of the trifluoroethoxy group enhances the electrophilic character of the phosphorus atom of phosphonate **204**, which Ando later proposed accelerates the ring-closing step to form the oxaphosphetane, therefore reducing the possibility for the kinetic *syn*-oxaphosphetane to equilibrate to the thermodynamically-favoured *anti*-oxaphosphetane.[79]

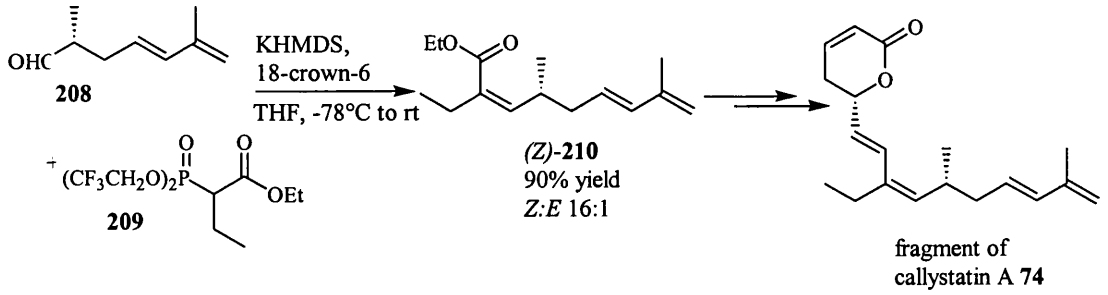
In support of this hypothesis, Still *et al.* has reported that *(E)*-isomer **207** was obtained from the reaction between benzaldehyde **95** and trimethyl phosphonate **151** under the same basic conditions used to produce *(Z)*-**205**, implying that the electron-withdrawing group of the phosphorus fragment is controlling the *(Z)*-stereochemistry of the product (Scheme 52).



95 **151** ***(E)*-207**
91% d.e.
83% yield

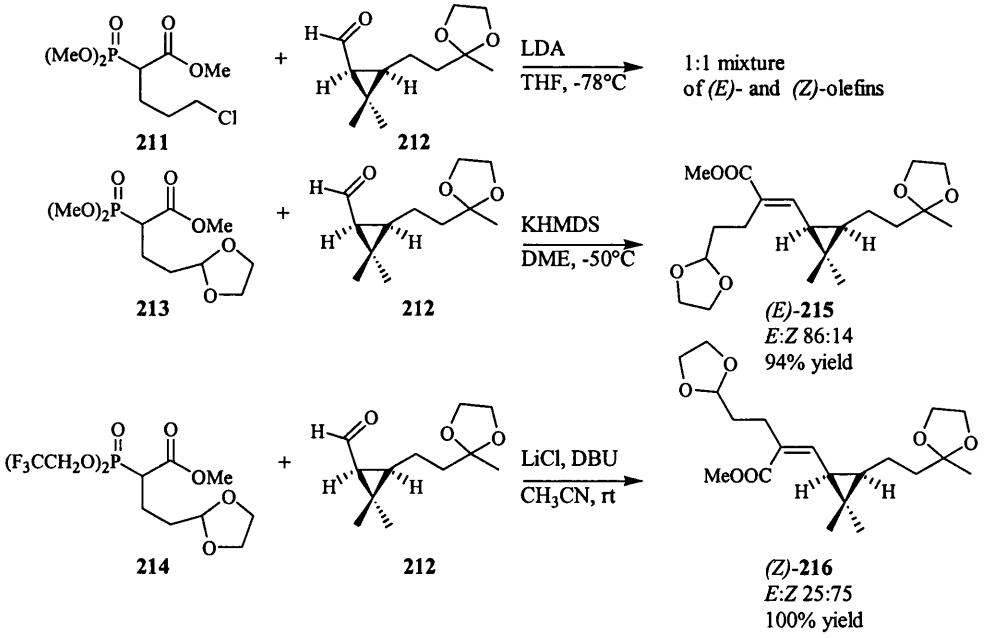
Scheme 52

Kobayashi *et al.* has reported that reaction of new α-ethyl HWE reagent **209** with α-substituted aldehyde **208** gave *(Z)*-α,β-unsaturated methyl ester **210** in a stereoselective fashion (Scheme 53).[80] This synthon was subsequently employed to determine the absolute stereochemistry of natural product callystatin A **74**.



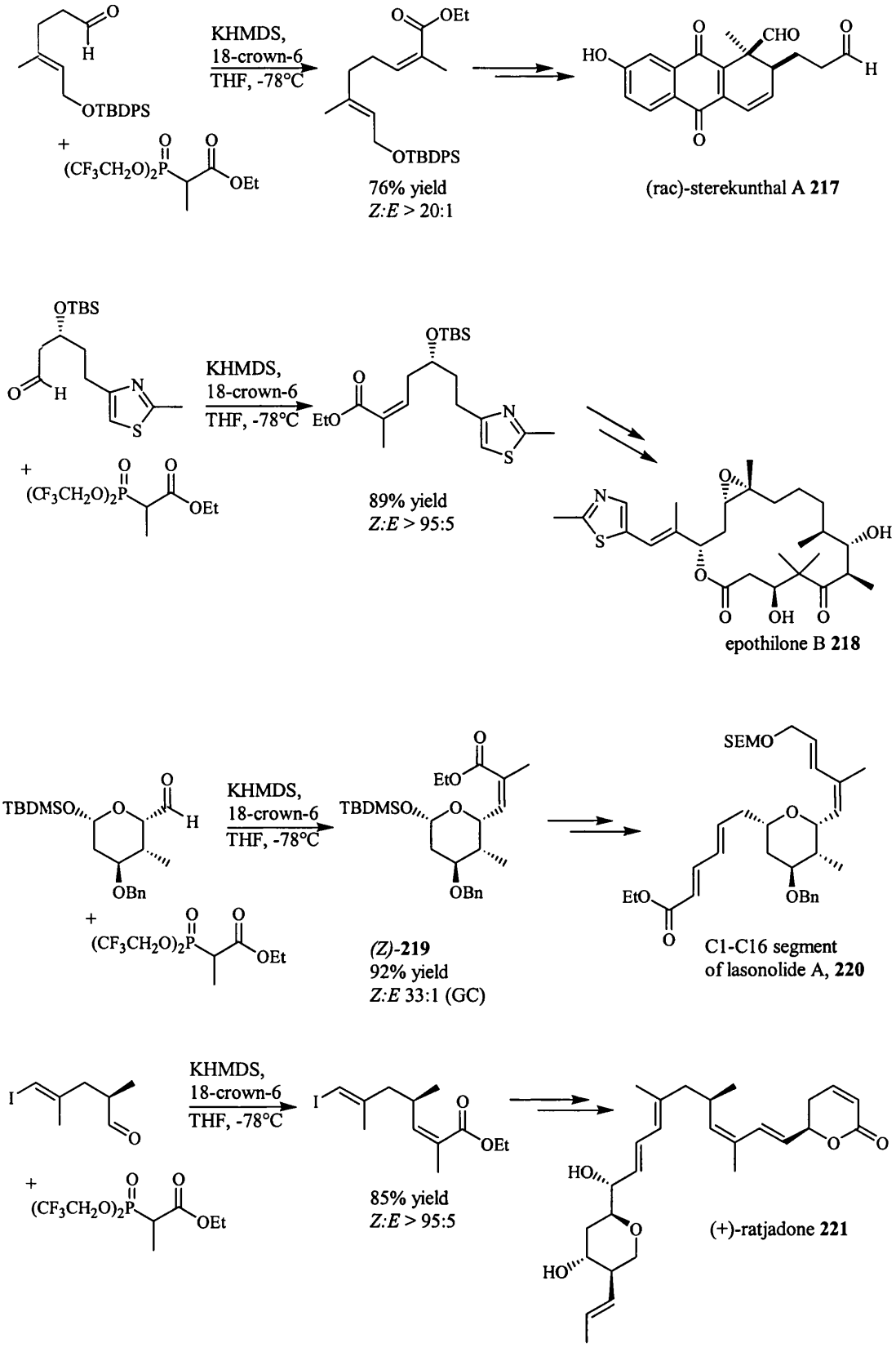
Scheme 53

Wiemer *et al.* experienced difficulties in carrying out a conventional HWE reaction using phosphonate **211** and aldehyde **212**, which proceeded with no stereocontrol to afford a 1:1 mixture of *(Z)*-and *(E)*-isomers.[81] They reasoned that reaction of aldehyde **212** with phosphonate **213** that contained a terminal acetal group would result in better selectivity *via* chelation of the acetal oxygen atoms to the lithium counteranion. Indeed, when phosphonate **213** was treated with lithium amide in the presence of LiCl at low temperature for 56 hours it gave selectively the *(E)*-isomer **215**. The potential of the trifluoroethylphosphonate methodology was further demonstrated, since treatment of aldehyde **212** with phosphonate **214** resulted in the formation of *(Z)*-**216** in 50% d.e. (Scheme 54).



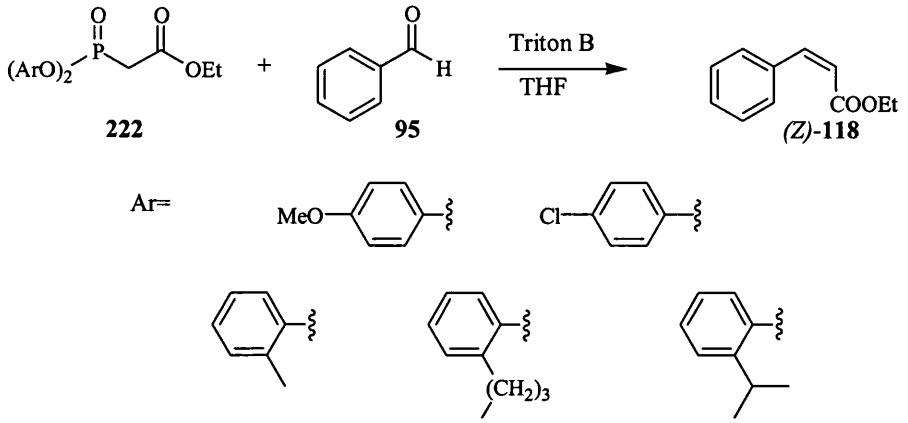
Scheme 54

This modification of the original HWE procedure has proven to be exceptionally popular in recent years for the preparation of *(Z)*-α,β-unsaturated carboxylic acid derivatives in the total synthesis of natural products, such as (rac)-sterekunthal A **217**, epothilone B **218**, lasonolide A **219**, and (+)-ratjadone **220** (Scheme 55).[82,83,84,85]



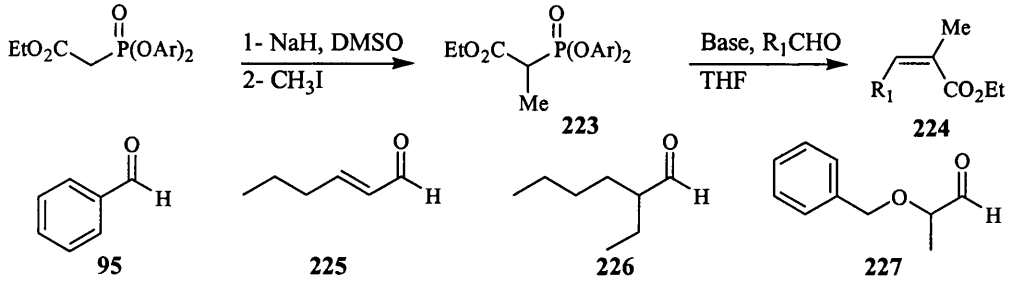
Scheme 55. Selected recent examples of application of the *(Z)*-selective HWE in the synthesis of natural products.

Ando first reported on an alternative procedure for the preparation of 2-disubstituted ethyl esters *(Z)*-**118** in a stereoselective manner using phosphonates in which the phosphorus atom is substituted with aryloxy groups.[79] The reaction of diphenylphosphonate **222** and benzaldehyde **95** afforded α,β-unsaturated ester *(Z)*-**118** in quantitative yield and 90% d.e. (Scheme 56). Electron-withdrawing or electron-donating groups on the aromatic group of the phosphonate did not affect the d.e., or yield of the reaction, whilst the presence of a bulky alkyl group substituent (methyl, ^{n}butyl and ^{i}propyl) in the ortho position of the aryloxy group was shown to improve the overall diastereoselectivity of the reaction.



Scheme 56

Ando has subsequently employed this approach for the preparation of trisubstituted *(Z)*-α,β-unsaturated esters **224** (Scheme 57, Table 2).[86] Substitution at the ortho position of the aryloxy substituent with a larger group once again improved the selectivity steadily from 90% d.e for Ar = Ph to 94% d.e. for Ar = *o*-^{i}PrPh (entry 1,2), whilst aldehydes substituted at the α-position also proceeded with good stereocontrol (entry 4, 5). However there were some limitations using this approach since reaction of phosphonate **223** with trans-2-hexenal **225** gave no products at –78°C.



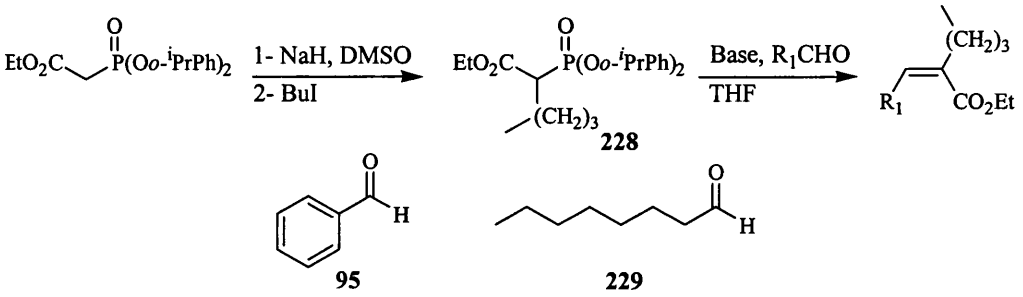
Range of aldehyde substrates

Scheme 57

	Base	Conditions	Ar	aldehyde	Yield (%)	*Z*:*E* ratio
1	^{t}BuOK	-95 to -78°C	Ph	**95**	98	95:5
2	^{t}BuOK	-95 to -78°C	*o*-^{i}PrPh	**95**	100	97:3
3	Triton B	-78 to 0°C	*o*-^{i}PrPh	**225**	95	89:11
4	NaH	-78 to 0°C	*o*-^{i}PrPh	**226**	95	99:1
5	NaH	-78 to 0°C	*o*-^{i}PrPh	**227**	79	98:2

Table 2

Ando has also reported on the reaction of α-butylphosphonate **228** with a range of aldehydes (Scheme 58, Table 3). Lower selectivities were obtained using Triton B and ^{t}BuOK, however use of NaH as base at –78°C improved the diastereoselectivity to 97% (Table 3, entry 1). Reaction with ^{n}octyl aldehyde **229** was the least selective affording increasing amounts of the thermodynamic product, the *(E)*-isomer, as the temperature was lowered (entry 2-4).



Range of aldehyde substrates

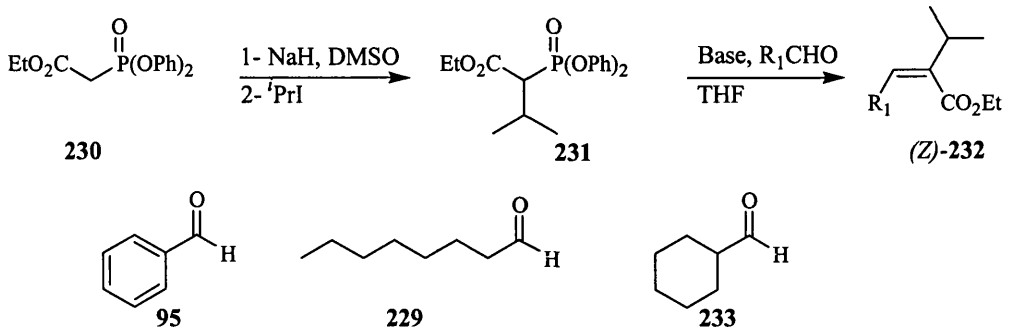
Scheme 58

	Base	conditions	aldehyde	Yield (%)	*Z*:*E* ratio
1	NaH	-78°C	**95**	95	97:3
2	NaH	0°C	**229**	94	83:17
3	NaH	-20°C	**229**	88	82:18
4	NaH	-40°C	**229**	58	69:31
5	^{t}BuOK	-78 to -40°C	**229**	69	12:88

Table 3

The sterically hindered ethyl-2-(diphenylphosphono)-3-methylbutanoate **231** was prepared by alkylation of ethyl (diphenylphosphono) acetate **230** with isopropyl iodide after treatment with NaH in DMSO (Scheme 59, Table 4). The reaction of the anion of **231** with benzaldehyde **95** initially gave poor yields of *(Z)*-**232** but good selectivity, however reaction at higher temperature was more successful (entry 1). Optimisation of the reaction

of phosphonate **231** with ^{n}octylaldehyde **229** (entry 2,3) or cyclohexanecarboxaldehyde **233** (entry 4) gave *(Z)*-olefins **232** with excellent selectivities but modest yields.

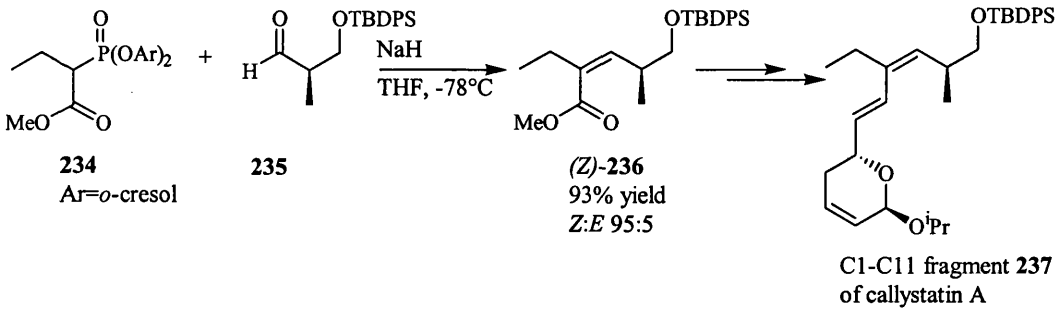


Scheme 59

entry	base	conditions	aldehyde	Yield (%)	*Z:E* ratio
1	NaH	0°C, 2h	**95**	96	99:1
2	NaH	-78°C-rt, 15h	**229**	61	93:7
3	NaH	0°C, 4h	**229**	75 (11)	91:9
4	NaH	-40°C, 4h	**233**	58	99:1

Table 4

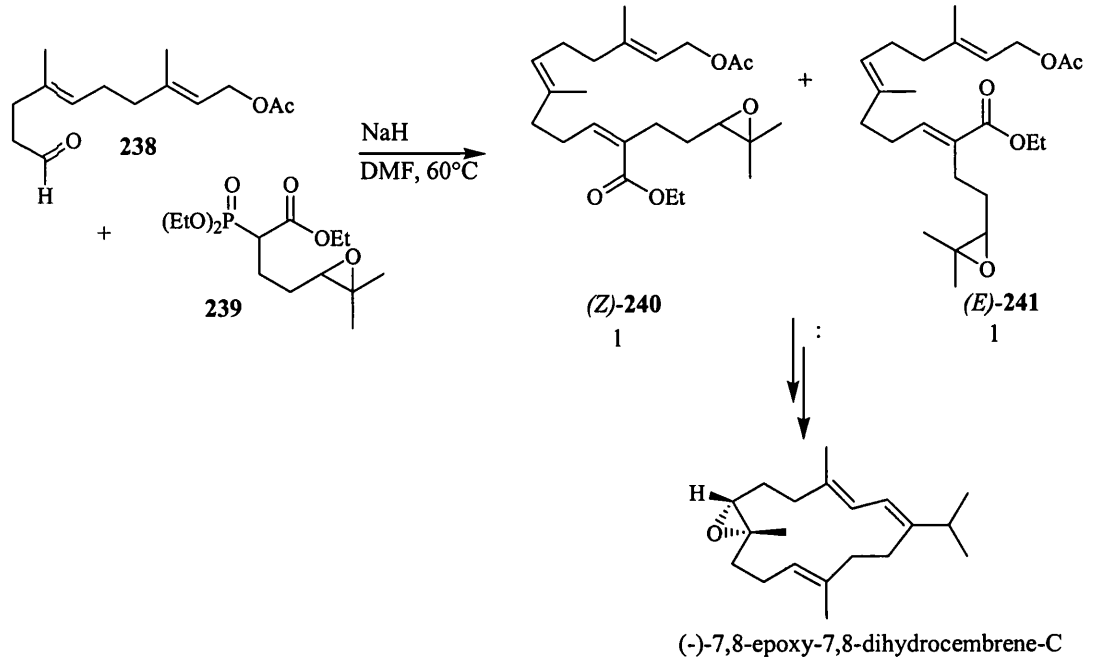
The potential of this methodology to afford *(Z)*-trisubstituted α,β-unsaturated esters in high diastereocontrol has also been demonstrated in natural product synthesis. For example, Dias *et al.* reported their efforts towards the enantioselective synthesis of C1-C11 fragment **237** of callystatin A.[87] Thus, reaction of labile aldehyde **235** and α-ethylphosphonoester **234** with sodium hydride afforded *(Z)*-trisubstituted-α,β-unsaturated ester **236** in 93% yield and 90% d.e. (Scheme 60).



Scheme 60

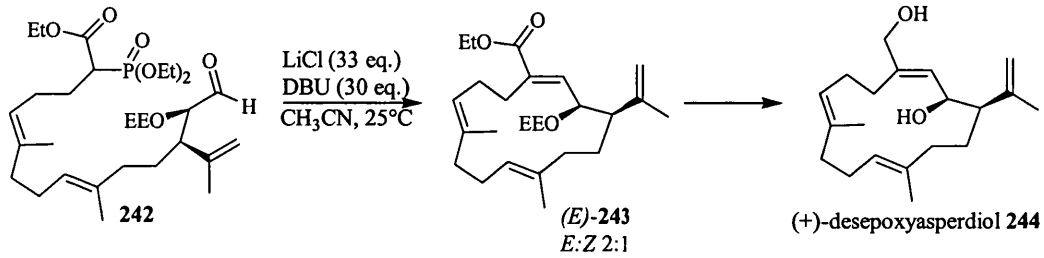
2.2.2.5 Limitations of the Wittig and HWE reaction

The Wittig and HWE reactions are very versatile procedures and now constitute a powerful tool for organic chemists who are involved in the total synthesis of natural products.[88] There are however some cases where the HWE reaction affords trisubstituted *(E)*-α,β-unsaturated esters with modest or no selectivity. For example, Li *et al.* have reported that reaction of aldehyde **238** with phosphonate **239** afforded a 1:1 mixture of isomers *(E)*-**240** and *(Z)*-**241** (Scheme 61).[89]



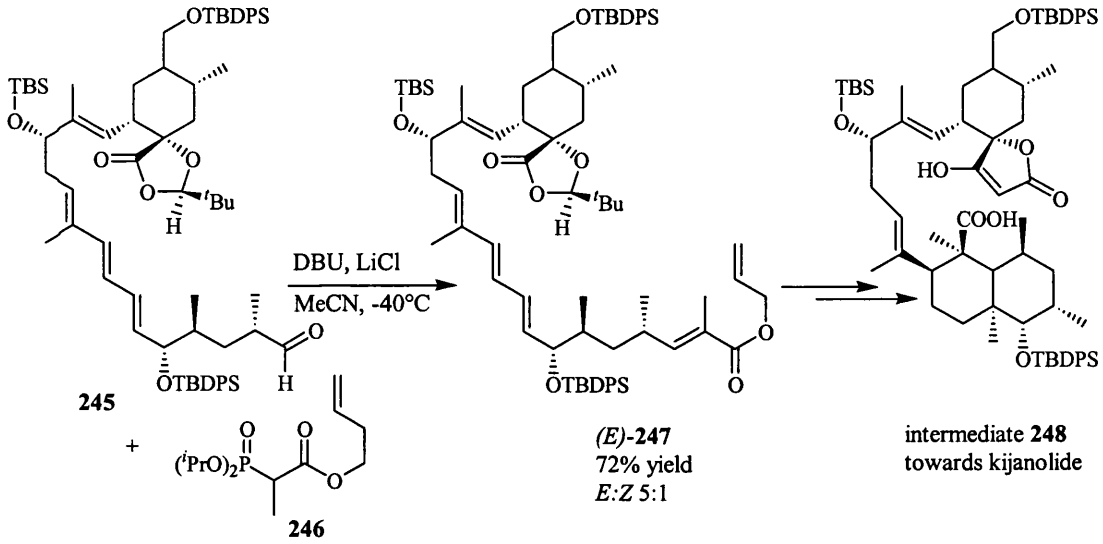
Scheme 61

Tius *et al.* have reported the use of intramolecular HWE methodology in the macrocyclisation of intermediate **242** in their route towards the enantioselective synthesis of cytotoxic (+)-desepoxyasperdiol **244**.[90] A variety of strong basic conditions (NaH, NaHMDS, $Li(O^iPr)_3$ and K_2CO_3/18-crown-6) failed to produce olefin **243** in significant quantities. However treatment of **242** under conditions originally reported by Masamune *et al.* did result in cyclisation to afford a 2:1 isomeric mixture of *(E)*-**243** and its *(Z)*-isomer in a combined 30% yield (Scheme 62).[67]



Scheme 62

The nature of the base used for deprotonation of the phosphonate, and the presence of additives, can also affect the selectivity of the reaction. Roush *et al.* has reported the synthesis of intermediate **247** toward the synthesis of kijanolide, involving olefination of the advanced aldehyde **245** with **246**.[91] However reaction of phosphonate **246** with KHMDS or LHMDS in THF at –78°C, followed by addition of aldehyde **245** gave poor diastereoselectivities for **247** with *E:Z* ratios ranging from 1:1 to 1.5:1. However the addition of lithium salts, as described by Masamune, Roush *et al.* enabled *(E)*-trisubstituted ester **247** to be obtained with much improved diastereocontrol (Scheme 63).

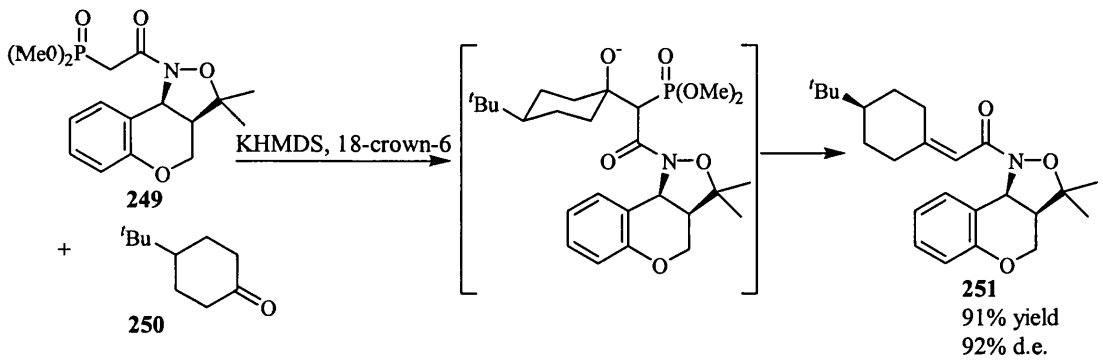


Scheme 63

2.2.2.6 Asymmetric Wittig reaction

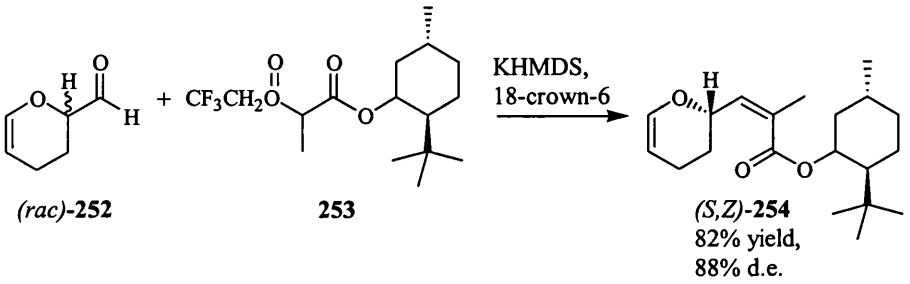
One of the major recent advances concerning the Wittig reaction has been made in studies of its asymmetric version. Several variations of this methodology have been described in order to induce asymmetry and these approaches have recently been reviewed by Rein *et al.*[92]

The first strategy involves desymmetrisation of a ketone with a chiral phosphonate reagent. For example, Abiko, Masamune *et al.* reported that reaction of prochiral ketone **250** with phosphonate **249**, containing a benzopyrano-[4,3-c]-iso-oxazolidine as chiral auxiliary afforded trisubstituted unsaturated amide **251** as a single enantiomer (Scheme 64).[93]



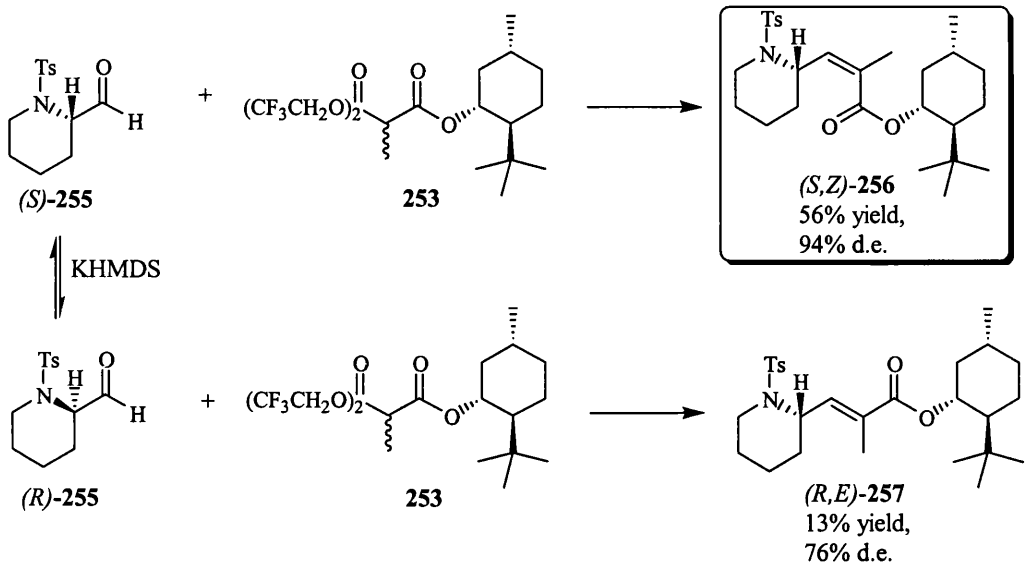
Scheme 64

Another strategy is kinetic resolution whereby a chiral reagent reacts selectively with only one enantiomer of a racemate. Reiser *et al.* have reported the use of 8-phenylmenthol-derived chiral auxiliary to selectively react with the *(S)*-enantiomer of aldehyde **252**. Thus reaction of racemic aldehyde **252** and the anion of chiral phosphonate **253** afforded *(S,Z)*-α,β-unsaturated ester **254** in a diastereoselective manner (Scheme 65).[94]



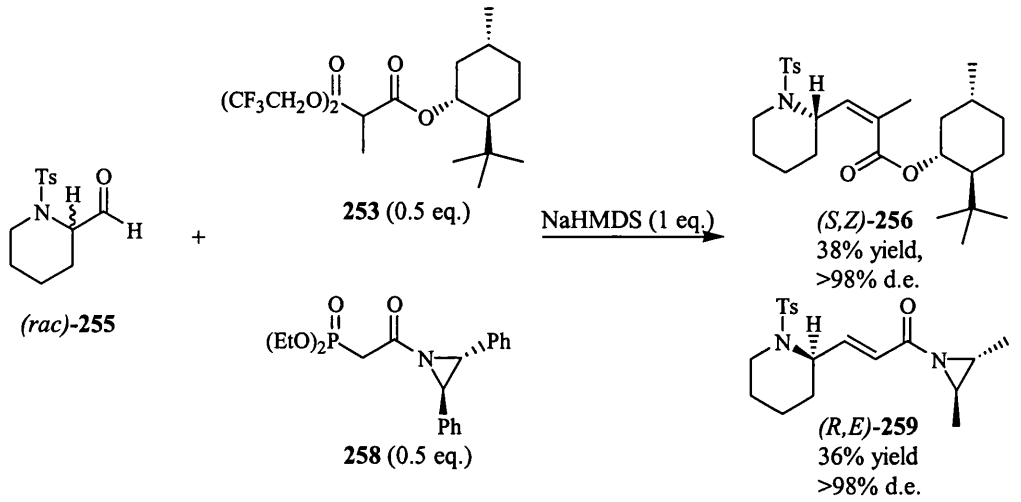
Scheme 65

The major drawback of kinetic resolution is the maximum yield obtainable that is 50%, therefore the racemic substrate needs to be present in at least a two-fold excess for complete conversion of the chiral reagent into the desired product. One solution is to carry out the reaction under conditions where the two enantiomers of the aldehyde substrate can interconvert. Rein *et al.* recognised that α-amino aldehydes are easily racemised and proposed that under the basic conditions used for the HWE reaction that amino aldehyde *(S)*-**255** would react preferentially with phosphonate **253** while enantiomer *(R)*-**255** would be racemised.[95] Thus, the reaction of 1 equivalent of racemic aldehyde **255** and 1.1 equivalent of chiral phosphonate **253** in the presence of 1 equivalent of KHMDS, afforded *(S,Z)*-olefin **256** as the major product in 56% yield and the "mismatched" *(R,E)*-olefin **257** in 13% yield (Scheme 66).



Scheme 66

An alternative strategy, which has also been used for the stereoselective synthesis of trisubstituted *(E)*-α,β-unsaturated esters was based on parallel kinetic resolution in which both enantiomers of a racemic aldehyde react with a different chiral reagent selectively to afford products that can be separated due to differences in physical properties imparted by their different chiral auxiliary fragments. Thus, Rein *et al.* have reported that reaction of 1 equivalent of racemic aldehyde **255** with 0.5 equivalent of *(Z)*-selective menthol-based phosphonate **253** and 0.5 equivalent of *(E)*-selective 1,2-diphenylaziridine-based phosphonate **258**, resulted in a mixture of olefins *(R,E)*-**259** and *(S,Z)*-**256** which were easily separated *via* chromatography (Scheme 67).[96]



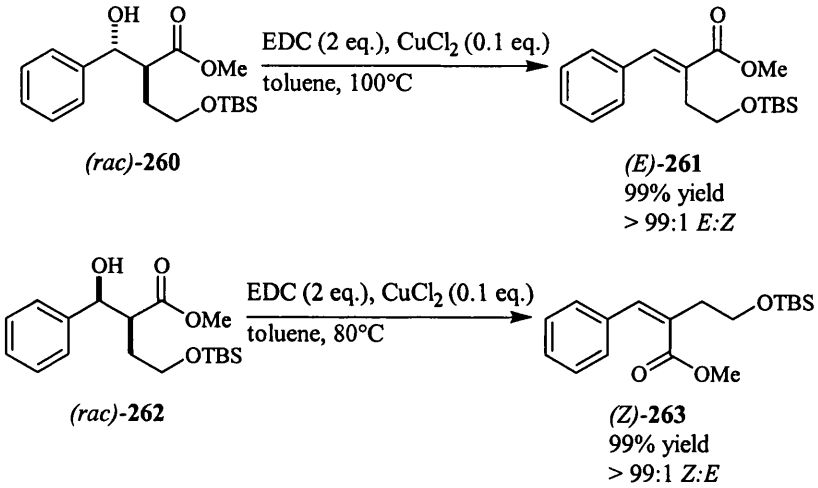
Scheme 67

2.23 Elimination reactions

Another type of procedure for affording α,β-unsaturated carboxylic acid derivatives is through the stereoselective elimination of β-hydroxyacid derivatives *via* E2-type eliminations pathways under kinetic control, or *via* E1-type mechanisms under thermodynamic control.

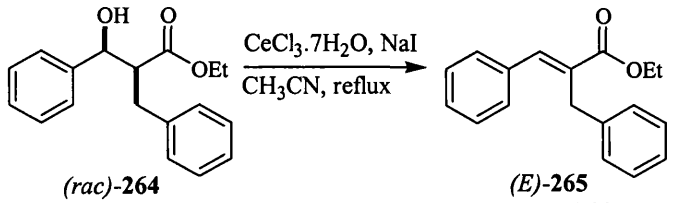
2.2.3.1 Dehydration reactions

Ohmizu *et al.* reported the highly stereoselective synthesis of *(E)*-α-substituted cinnamate **261** *via* treatment of *anti*-aldolate **260** with 1-ethyl-3-(3-dimethyl-aminopropylcarbodiimide) as a dehydrating agent.[97] Alternatively the *(Z)*-α-substituted cinnamate ester **263** was generated from dehydration of the corresponding *syn*-aldolate **262** (Scheme 68). It should be noted that the selectivity observed in these elimination reactions is opposite to that expected if an E2 mechanism was in operation.



Scheme 68

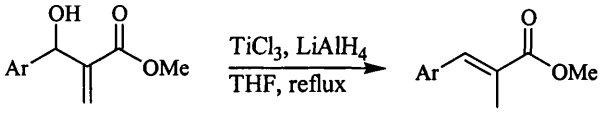
Bartoli, Mercantoni *et al.* have also developed an efficient procedure for the diastereoselective dehydration of aldolate compounds using a mixed $CeCl_3.7H_2O$/NaI system.[98] For example β-hydroxy ester **264** was dehydrated to afford cinnamate ester *(E)*-**265** in excellent yield and as the sole isomer. No mechanism has been proposed to explain the selectivity of this remarkable elimination reaction, however it should be noted that no reaction occurred in the absence of sodium iodide.



(rac)-**264** *(E)*-**265**
90% yield
> *E:Z* 95:5

Scheme 69

Nayak *et al.* reported the reductive dehydroxylation of Baylis-Hillman adducts which afforded the thermodynamically more stable *(E)*-cinnamate esters.[99] Thus, aldolate **266** in the presence of the strong Lewis acid $TiCl_3$ and reducing agent $LiAlH_4$ in refluxing THF afforded *(E)*-α,β-unsaturated ester **267** in a stereoselective fashion but only in a modest yield (Scheme 70, Table 5).



(rac)-**266** *(E)*-**267**

Scheme 70

	Ar	Yield (%)	*E:Z*
1	Ph	46	88:12
2	*p*-MeOPh	46	87:13
3	3,4-(CH_2O)Ph	41	92:8
4	2-furfuryl	50	96:4

Table 5

Titanium is oxophilic and will chelate between the β-hydroxyl group and the carbonyl oxygen of the ester inducing some selectivity into the reduction/elimination process. Transition state **270** results in a large steric crowding between the β-aromatic and alkoxy group of the ester, favouring transition state **268**, which led to the formation of *(E)*-**267** after rapid H-capture from radical **269** (Figure 18).

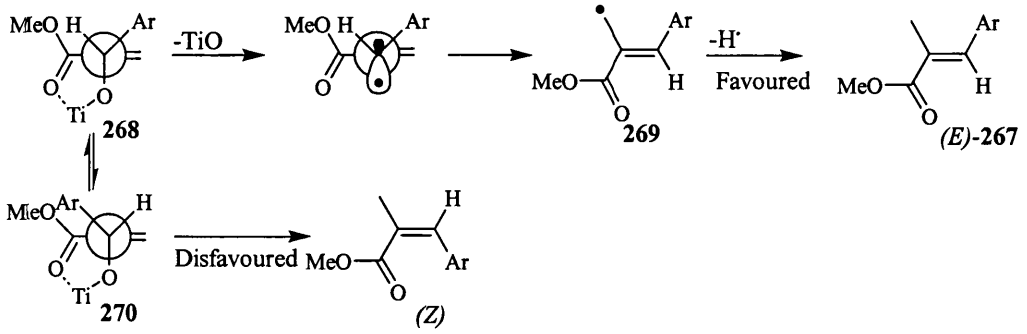
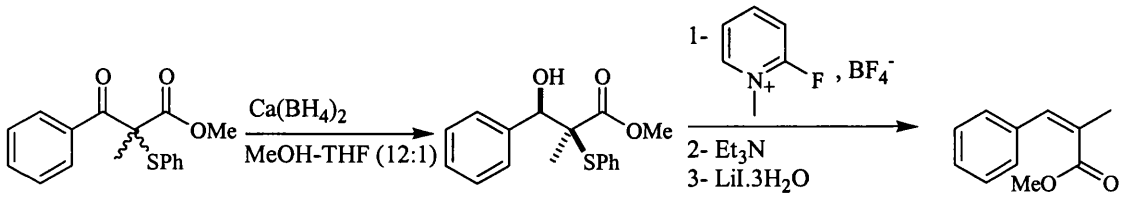


Figure 18

2.2.3.2 Elimination of thioalcohols

The elimination of *syn*-β-hydroxy-α-phenylthio esters to afford unsaturated esters *via* E2 elimination had been reported by a number of groups,[100] however the starting *syn*-α-thioaldolates were not easily prepared.[101] Shimagaki *et al.* reported that facile reduction of β-ketoester **271** afforded the desired *syn*-aldolate **272** in excellent yield and in a stereoselective fashion.[102] E2 elimination of the thioester **272** then occurred readily to afford selectively the isomer *(Z)*-**273** (Scheme 71).

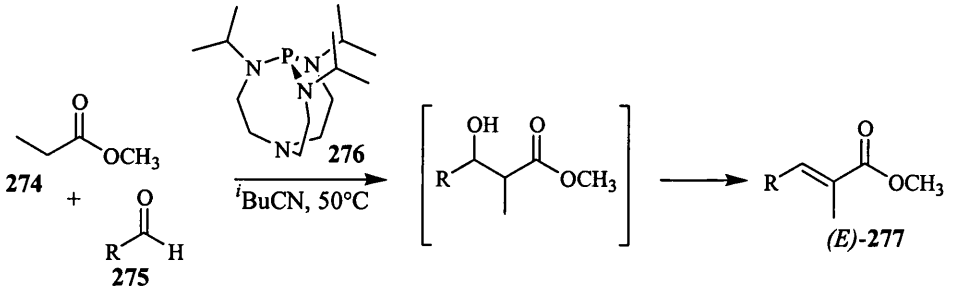


271 *(rac)*-**272** *(Z)*-**273**
81% yield
Z:E 97:3

Scheme 71

2.2.3.3 Aldol condensation and elimination

Verkade *et al.* have reported on the efficient preparation of *(E)*-α-methyl-α,β-unsaturated methyl esters **277** in the presence of pro-azaphosphatane **276** *via* aldol condensation of aromatic aldehydes **275** and methyl propionate **274** followed by *in-situ* dehydration of the resultant aldolate.[103] Thus, this reaction afforded *(E)*-unsaturated esters **277** in excellent yield and as essentially single stereoisomers (Scheme 72, Table 6). It is noteworthy that Verkabe proved that the base **276** could be recovered at the end of the reaction in 81% yield, thereby demonstrating that the only by-product of this reaction is water.



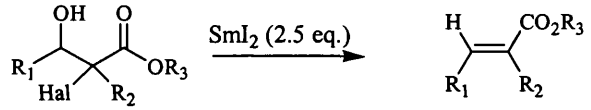
Scheme 72

	R	Yield (%)
1	Ph	93
2	*p*-ClPh	95
3	*p*-MeOPh	68
4	*o*-MeOPh	87
5	furyl	83

Table 6

2.2.3.4 Elimination of halogen with SmI_2

Concellón *et al.* have reported that samarium iodide is a highly efficient reagent for promoting the β-elimination of a wide range of α-halo-β-hydroxyesters **278** and **279**, yielding high yields of trisubstituted unsaturated esters **280** with consistently high *(E)*-selectivities.[104] Aliphatic, unsaturated and aromatic aldehydes could be employed as substrates, whilst the size of the alkyl group on the carboxyl ester did not effect the selectivities. Better conversions were obtained when SmI_2 was formed *in situ* by adding diiodomethane (2.5 eq.) to a suspension of samarium metal (2.5 eq.) and 2-halo-3-hydroxyesters **278** and **279** in THF at room temperature (Scheme 73, Table 7).[105]



syn-**278** and *anti*-**279** *(E)*-**280**

Scheme 73

	R_1	R_2	R_3	Hal	d.e. %	Yield %[b]
1	$CH_3(CH_2)_6$[a]	H	Me	Cl	88	30
2	$CH_3(CH_2)_6$	Me	Et	Cl	>98	94 (75)
3	Cyclohexyl	Me	Et	Cl	>98	93 (90)
4	*p*-ClC_6H_4	H	^{t}Bu	Cl	>98	45 (72)
5	Ph	Bu	Et	Br	>98	90 (86)
6	*p*-MeO-C_6H_4	Me	Et	Cl	>98	95 (91)
7	$Me_2C{=}CH(CH_2)_2CHMeCH_2$	Ph	^{i}Pr	Cl	>98	97 (84)

[a] Performed with O-acetylated compound rather than the unprotected alcohol; [b] Yields of the products when using preformed SmI_2 are shown in brackets.

Table 7

Concellón proposed a chelation-control model to account for the observed stereoselectivity in which a samarium enolate intermediate **281** is formed. Chelation of the oxophilic Sm^{III}

centre to the oxygen atom of the β-hydroxyl group produced a six-membered ring **281** thus increasing the leaving group ability of the hydroxyl group. In chair-like transition state **A** the bulky alkyl group R_1 occupies the more favoured equatorial position resulting in a *cis* relationship between R_2 and R_1 and consequently elimination affords *(E)*-α,β-unsaturated esters. This mechanism also explains why O-acetylated β-hydroxy ester (entry 1) was eliminated in poor yield in relatively low d.e. (Figure 20).

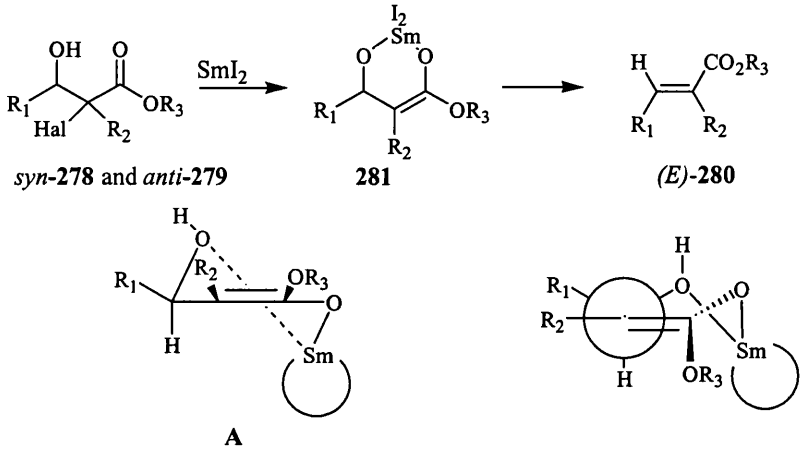
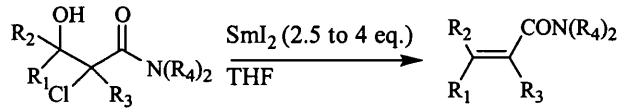


Figure 19. Mechanistic proposal for the elimination of 2-halo-3-hydroxyesters with SmI_2

Using essentially the same methodology the reaction of 2-chloro-3-hydroxyamides *syn*-**282** and *anti*-**283** with SmI_2 afforded mixed results (Scheme 74, Table 8).[106] Disubstituted unsaturated amides *(E)*-**284** (entry 1) were prepared in good yield and with good *(E)*-selectivity. Lower diastereoselectivities and poorer conversions were observed in attempting to prepare trisubstituted unsaturated amides *(E)*-**284** (entry 2) but an increase in the loading in the Lewis acid resulted in high to excellent *(E)*-selectivities (entries 3-5).

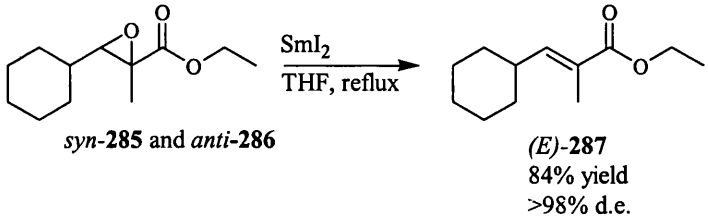


Scheme 74

	R_1	R_2	R_3	R_4	T (°C)	eq.SmI_2	d.e.	Yield %
1	MeCHPh	H	H	Ph	25	2.5	> 98	90
1	Ph	H	Me	Et	25	2.5	89	51
2	Ph	H	Me	Et	-25	4	> 98	88
3	*p*-$MeOC_6H_4$	H	Me	^{i}Pr	-25	4	93	75
4	cyclohexyl	H	Me	Et	-25	4	> 98	95
5	^{n}heptyl	H	Me	Et	-25	4	> 98	81

Table 8

Finally Concellón *et al.* reported last year that SmI_2 could be used to promote the elimination of epoxyesters *syn*-**285** and *anti*-**286** to yield α,β-unsaturated ester *(E)*-**287** with high *(E)*-selectivities and good yields (Scheme 75).[107]



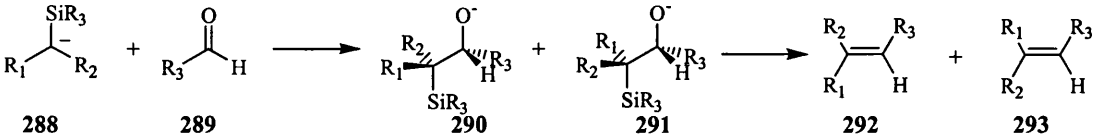
syn-**285** and *anti*-**286**

(E)-**287**
84% yield
>98% d.e.

Scheme 75

2.2.3.5 The Peterson olefination

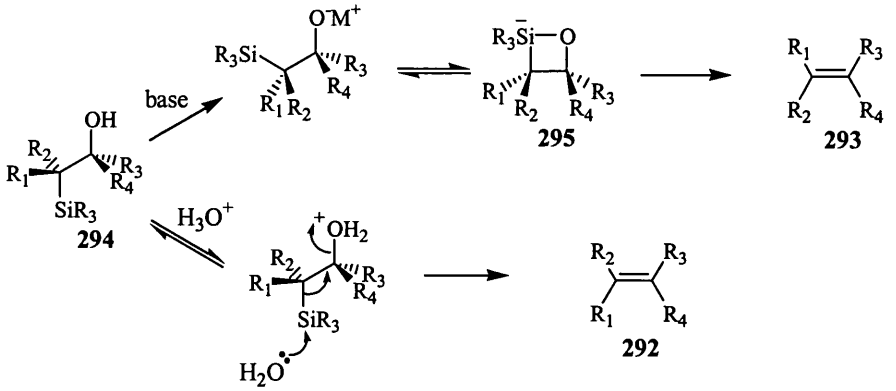
The Peterson olefination is often seen as the silicon analogue of the Wittig reaction in which a silyl carbanion **288** attacks an electrophilic aldehyde **289** (or a ketone) to afford a mixture of β-hydroxysilanes **290** and **291**, which can then eliminate to afford either olefins **292** and **293** (Figure 20).



288 **289** **290** **291** **292** **293**

Figure 20

The elimination of β-hydroxysilane **294** is stereoselective and depends on the conditions employed for elimination. Acid-promoted elimination occurs *via* an *anti*-periplanar mechanism to afford olefin **292**, while treatment of β-hydroxysilane **294** with base occurs *via* the 4-membered species **295** and affords olefin **293**. Therefore, both geometric isomers can potentially be prepared from the same β-hydroxysilane **294**, depending on the conditions employed for elimination (Figure 21).

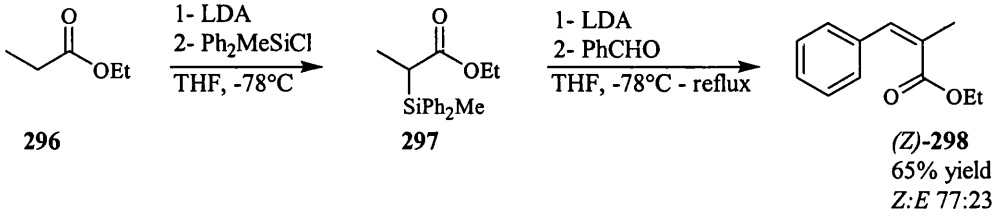


294 **295** **293** **292**

Figure 21

For the specific cases of silyl carbanions stabilised with an electron-withdrawing group it has usually not been possible to isolate β-hydroxysilanes intermediates since they spontaneously eliminate to afford the α,β-unsaturated acid derivatives.

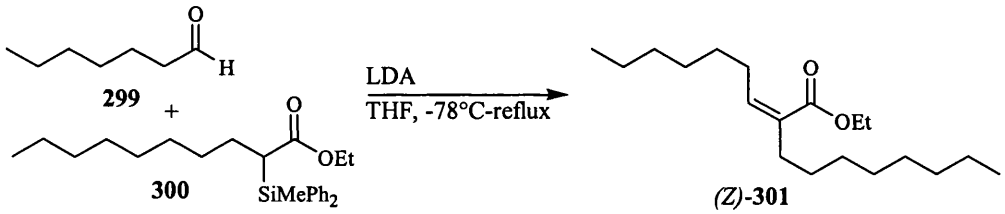
Larson *et al.* reported that silylation of the lithium enolate of ester **296** afforded silyl ester **297**.[108] Further deprotonation, addition of benzaldehyde and *syn*-elimination afforded *(Z)*-unsaturated ester **298** in modest yield and selectivity (Scheme 76).



296 **297** *(Z)*-**298** 65% yield *Z:E* 77:23

Scheme 76

The length of the alkyl group on the phosphonate in the Wittig reaction and its variations can dramatically decrease the overall stereoselectivity (see section 2.2.2.5). Larson *et al.* found that the Peterson olefination of the lithium enolate of silyl ester **300** and aldehyde **299** afforded the unsaturated ethyl ester *(Z)*-**301** once again with only modest selectivity (Scheme 77).

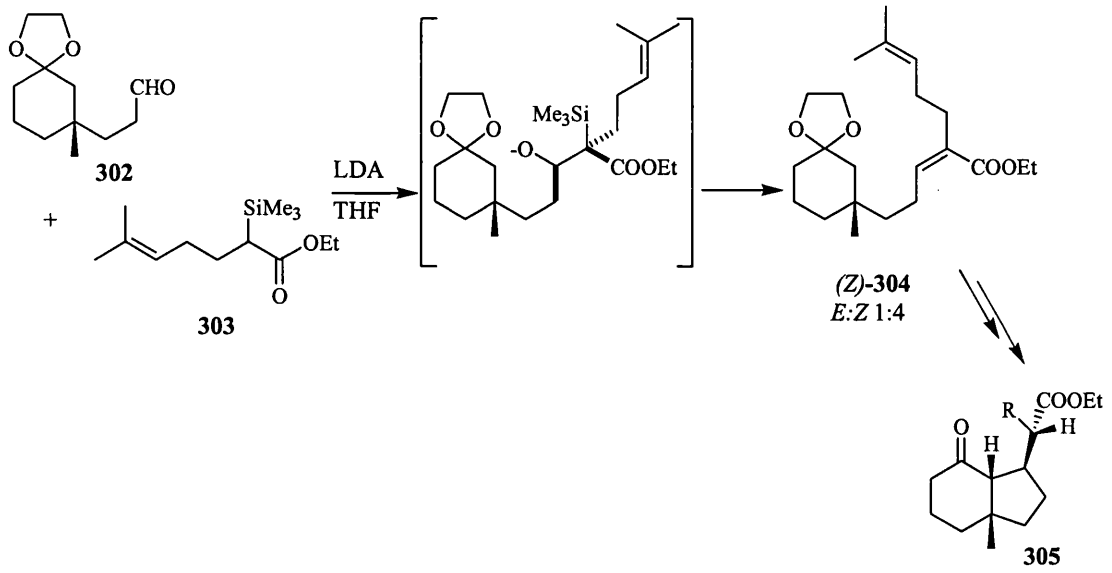


299 + **300**

(Z)-**301** 62% yield *Z:E* 71:29

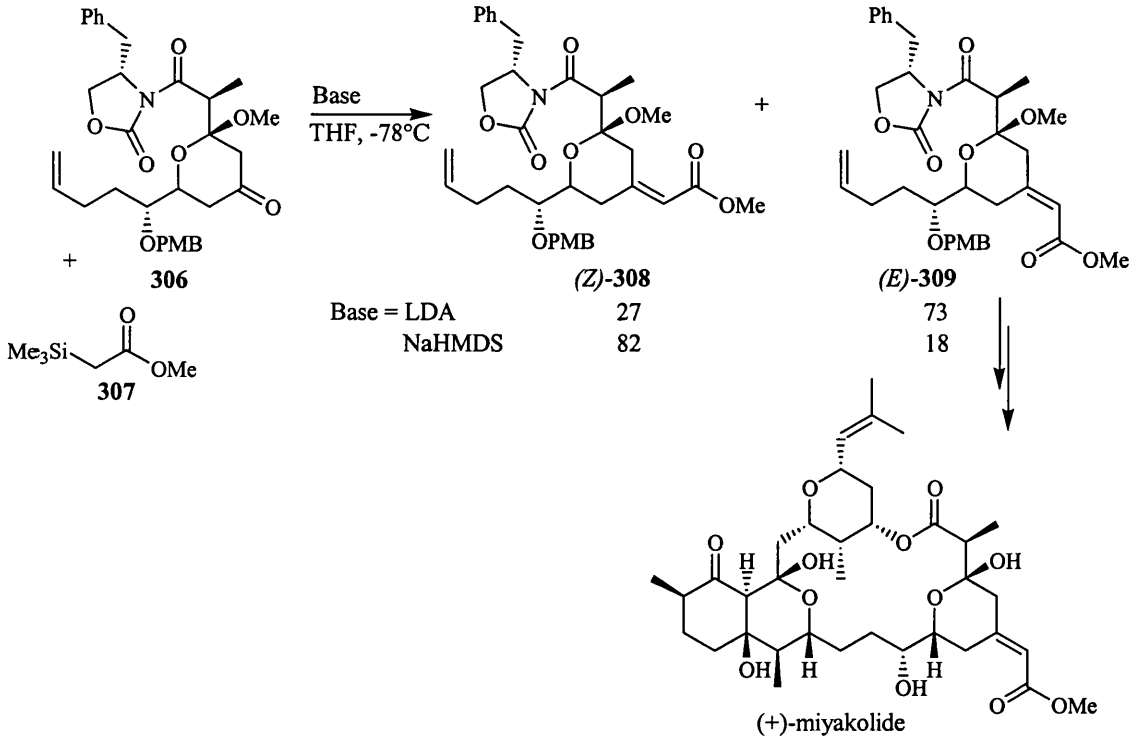
Scheme 77

In 1996 Hart *et al.* prepared acetal-protected cyclohexanone **304** *via* Peterson olefination as a target on his route to terpenoid **305**.[109] Thus, the reaction of lithium enolate of α-trimethylsilylethylester **303** and aldehyde **302** afforded unsaturated ester *(Z)*-**304** in moderate yield and selectivity (Scheme 78).



Scheme 78

Finally in 1999 Evans *et al.* elected to use the Peterson reaction for olefination of ketone **306** as an alternative to the HWE reaction, which was found to afford the opposite *(Z)*-selectivity.[110] Thus, the reaction of cyclic ketone **306** and methyl (trimethylsilyl)acetate **307** with LDA in THF at –78°C gave α,β-unsaturated ester *(E)*-**309** in 99% yield and 46% d.e. It is noteworthy that if NaHMDS was employed in THF the stereoselectivity was inverted and *(Z)*-**308** was afforded in 64% d.e. (Scheme 79).



Scheme 79

2.2.4 Palladium coupling

2.2.4.1 The Heck reaction

Another means of preparing trisubstituted α,β-unsaturated esters containing β-aryl substituent is *via* the Heck reaction involving the coupling of an aryl halide or triflate and a disubstituted α,β-unsaturated ester in the presence of palladium catalyst and a base.

The Heck reaction is initiated by oxidative addition of halide **311** to a palladium Pd(0) species **310**, the resulting vinyl (or aryl) palladium Pd(II) intermediate **312** then forms a π-complex with the alkene **313**, which rearranges to σ-complex **314** resulting in carbon-carbon bond formation. σ-Complex **314** decomposes by β-elimination to afford the coupled product **316** and the Pd(II) catalyst species **315** which is eliminated by a base to regenerate Pd(0) species **310** (Figure 22).

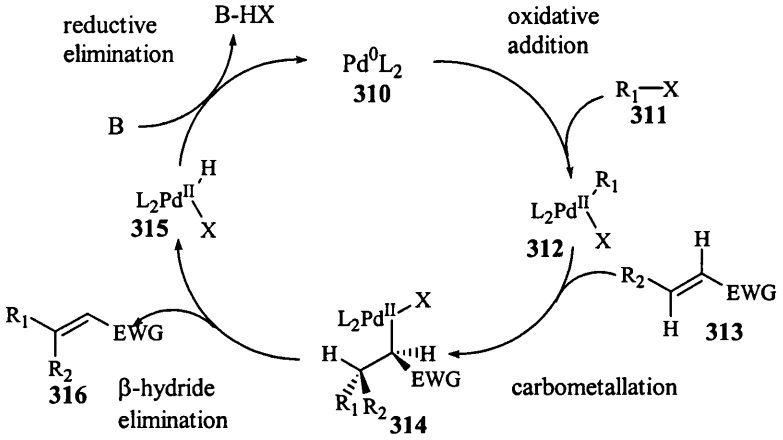
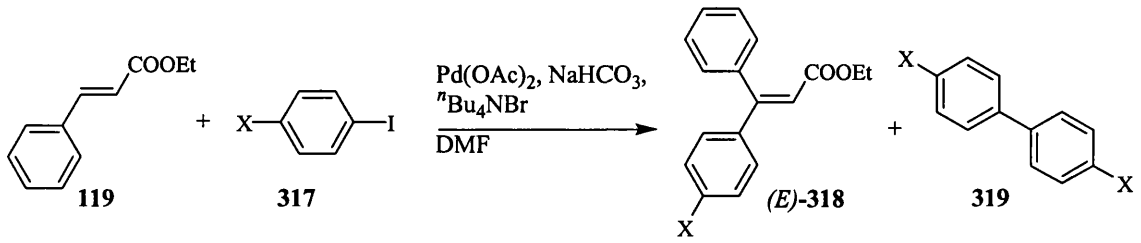


Figure 22

Unlike the preparation of disubstituted α,β-unsaturated carboxylic acid derivatives, using this methodology, reports on the stereo and regioselective synthesis of trisubstituted esters are relatively rare. Moreno-Mañas *et al.* have reported that β,β-diarylpropenamides *(E)*-**318** could be prepared using the Heck reaction, affording *(E)*-esters as major products for both electron-donating and electron-withdrawing aryl iodides **317** (Scheme 80, Table 9).[111] A palladium-iodo complex added to alkene **119** in a stereoselective fashion to afford *(E)*-**318**, although *E*/*Z* isomerisation was observed as the temperature of the reaction was increased (entry 2). With electron-withdrawing substituents in the *para*-position some biaryl products **319** were also observed (entry 4).



119 317 (*E*)-318 319

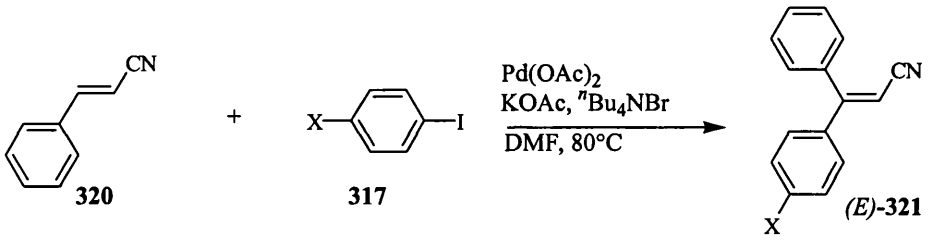
Scheme 80

	X	Time (days)	T (°C)	Yield (%)	*E:Z*
1	OMe	8	60	73	83:17
2	OMe	2	120	81	64:33
3	Me	2	80	67	100:0
4	CF_3	9	60	19[a]	100:0

[a] 4,4'Bis(trifluoromethyl)biphenyl (6% yield) was also isolated.

Table 9

Moreno-Mañas *et al.* reported a year later that the equivalent nitrile *(E)*-**321** could also be obtained in improved yield and stereoselectivity using cinnamonitrile **320** as a coupling partner under related conditions (Scheme 81, Table 10).[112]



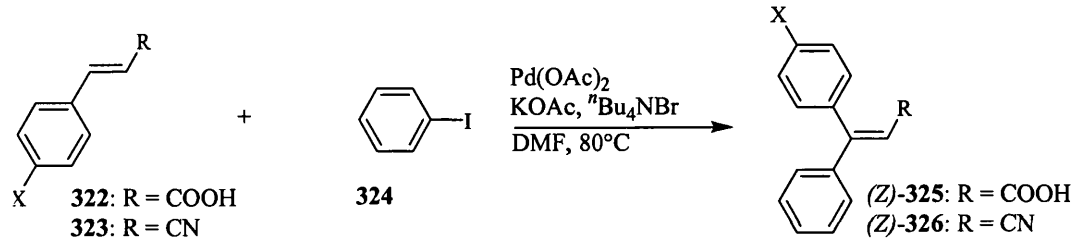
320 317 (*E*)-321

Scheme 81

	X	Yield (%)	% recovered 320
1	NH_2	78	-
2	CH_3	80	9
3	Cl	55	29

Table 10

The same research group has also reported on the alternative preparation of *(Z)*-β,β-diarylpropenacids *via* addition of iodobenzene **324** to substituted cinnamate substrates **322** and **323**,[111] however they once again found that cinnamonitriles **323** were more stable under the reaction conditions affording *(Z)*-α,β-unsaturated nitrile **326** in improved yield and selectivity (Scheme 82, Table 11).[112]



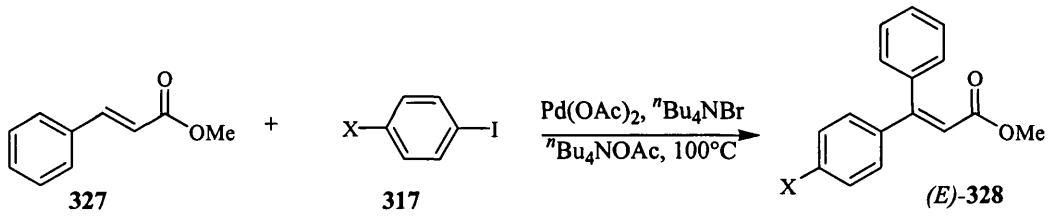
Scheme 82

	X	(*Z*)-**325**		(*Z*)-**326**	
		Yield (%)[a]	***Z:E***	**Yield (%)**[a]	***Z:E***
1	MeO	47 (41)	98:2	76	> 99:1
2	CH_3	66	89:11	75 (13)	> 99:1
3	CF_3	75 (2)	75:25	74 (14)	> 99:1

[a] yields of pure isolated products, between brackets % of unreacted starting material

Table 11

Cacchi *et al.* have recently reported improved stereoselectivity and yields for the preparation of this type of trisubstituted acid derivatives using a molten $^{n}Bu_4NOAc/^{n}Bu_4NBr$ mixture. Thus, the Heck reaction of methyl cinnamate ester **327** and aryl iodide **317** afforded coupling product *(E)*-**328** (Scheme 83, Table 12).[113]

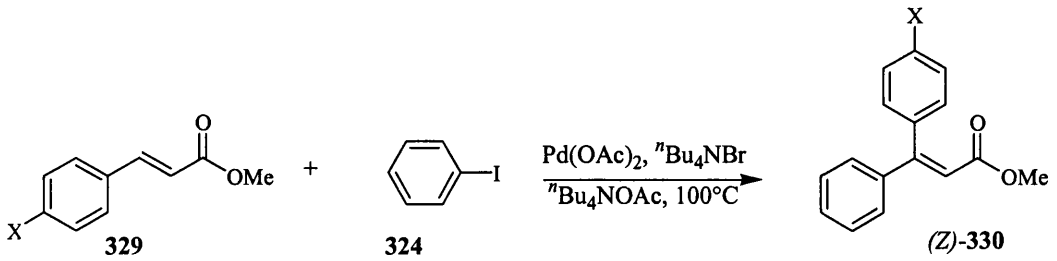


Scheme 83

	X	**Time (hours)**	**Yield (%)**	***E:Z***
1	*p*-OMe	3	80	>99:1
2	*p*-Me	3.5	82	99:1
3	*m*-Me	7	80	99:1
4	*p*-COOEt	9	38	98:2

Table 12

Under the same conditions the reaction of 3-arylacrylates **329** and iodobenzene **324** was also shown to afford *(Z)*-*β*,*β*-diarylpropenester **330** in a diastereoselective fashion (Scheme 84, Table 13).

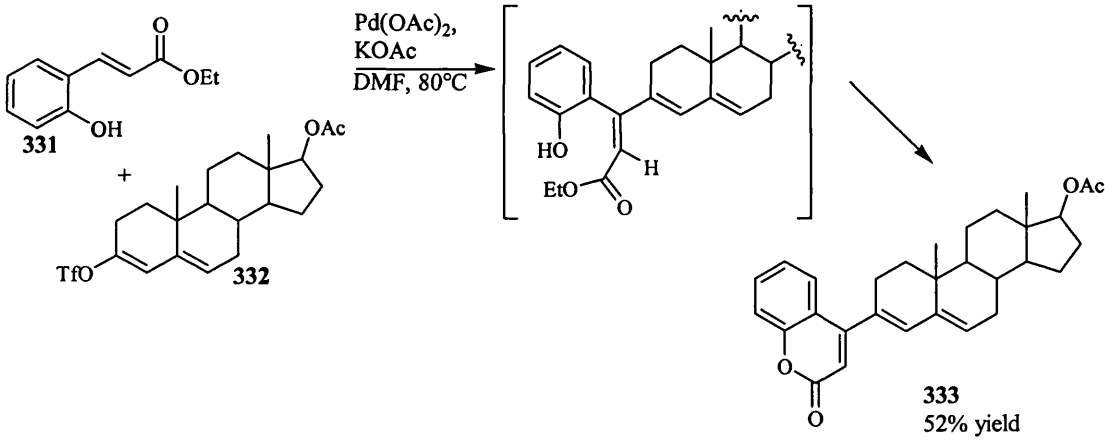


Scheme 84

	X	Time (hours)	Yield (%)	*E:Z*
1	*p*-OMe	4	78	2:98
2	*p*-Me	3.5	72	> 1:99
3	*m*-Me	6	70	1:99
4	*p*-COOEt	3.5	84	4:96

Table 13

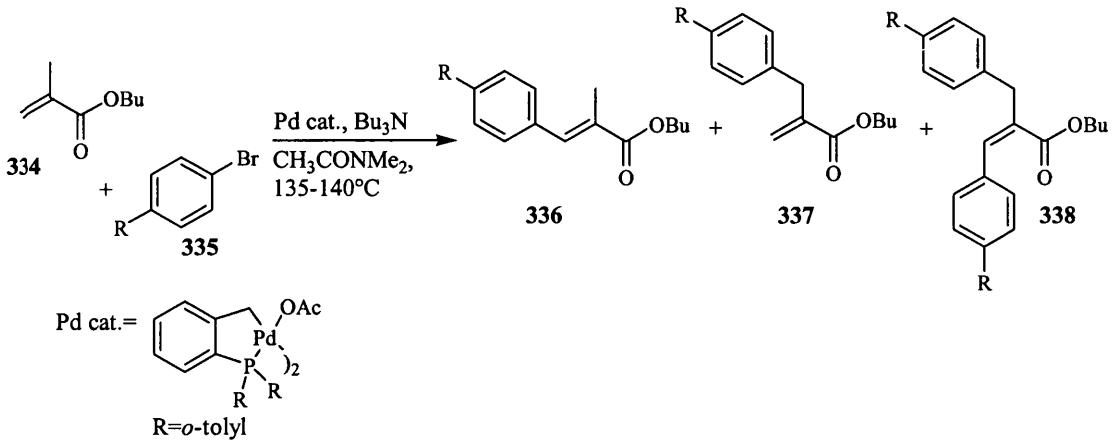
Coupling of disubstituted unsaturated esters with vinyl triflates has also been shown to afford *(E)*-esters in high d.e.[114] Cacchi *et al.* have reported the application of this approach to the preparation of substituted coumarin **333** *via* coupling reaction of cinnamo ester **331** and vinyl triflate **332** (Scheme 85).[115]



Scheme 85

There are few examples where the Heck reaction between methacrylate esters and aryl halide has been successfully realised despite the potential of α-methyl-substituted cinnamic acid derivatives as a building block for organic synthesis. Beller *et al.* attempted to carry out this transformation using butyl methacrylate ester **334** and aryl bromides **335** as substrates (Scheme 86, Table 14).[116] Reaction using sodium acetate as a base afforded no selectivity between the formation of **336** and **337**, whilst longer reaction times (entry 1) resulted in the formation of disubstituted **338**. However, reaction with tributylamine was shown to afford the desired trisubstituted α,β-unsaturated ester *(E)*-**336** with improved

selectivity (entry 2), whilst higher catalyst loading also afforded better conversion of substrates to product (entry 3). Other electron withdrawing aryl halides afforded trisubstituted ester *(E)*-**336** in a selective fashion and in good yield (entries 4 and 6), however, whilst the reaction with electron-donating arylhalides was both stereo and regioselective, it did not go to completion with 75% of starting material being recovered, for R = OCH_3 (entry 5).



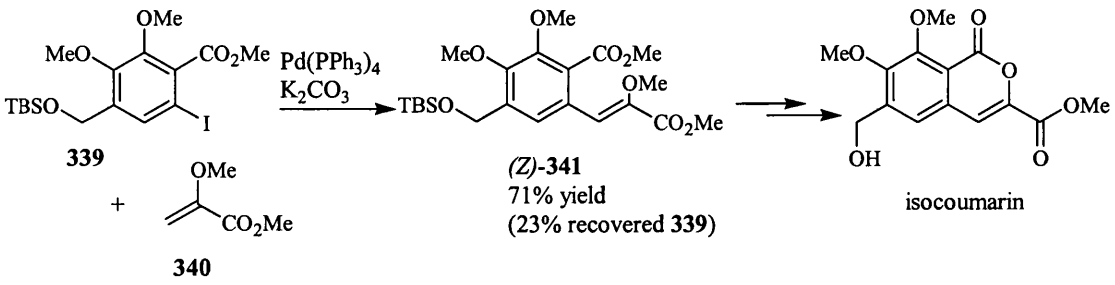
Scheme 86

	R	336 : 337 : 338	Yield (336 + 337)
1	F[a,b]	1.4 : 1 : 1.2	31
2	F[a]	3.9 : 1 : 0.2	12
3	F	9.3 : 1 : 1.5	60
4	$COCH_3$	11.5 : 1 : 2.1	74
5	OCH_3	4.9 : 1: < 0.1	20
6	NO_2	8.1 : 1 : 0.7	75

[a] Pd cat at 0.01%; [b] base used NaOAc.

Table 14.

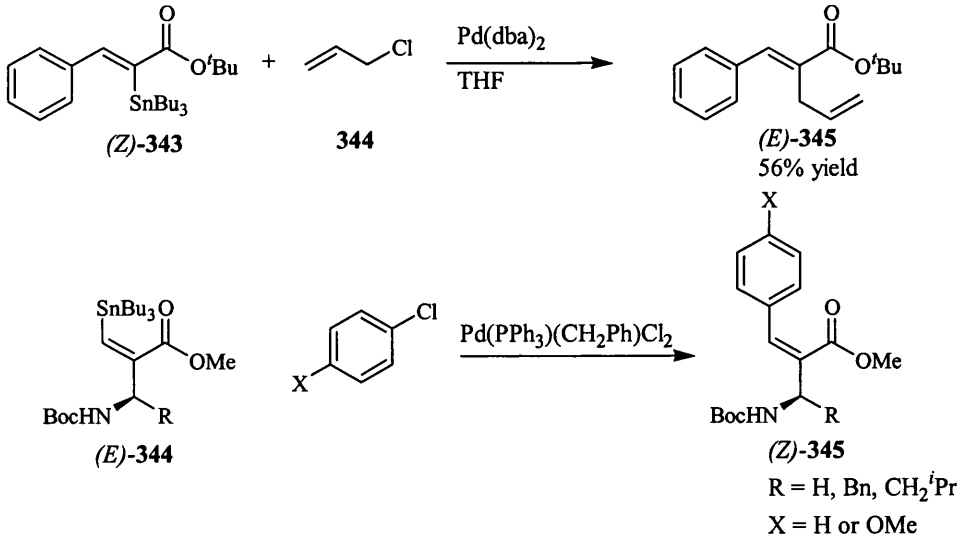
Kozlowski *et al.* reported in 2001 on the synthesis of the isocoumarin portion of the rubromycins, a class of natural products that exhibits antibiotic properties.[117] The isocoumarin ring system **341** was formed *via* Heck coupling of a masked pyruvate synthon **340**, and iodo-terephtalic acid derivative **339** with good d.e. followed by an intramolecular acid-catalysed cyclisation (Scheme 87).



Scheme 87

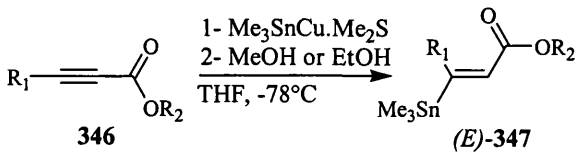
2.2.4.2 Cross-coupling of organostannanes

α,β-Unsaturated esters that contain stannane substituents at either their α- or β-positions are versatile synthons for the preparation of aryl substituted α,β-unsaturated esters *via* Stille coupling protocols. For example the Stille reaction of tributyl stannane *(Z)*-**343** and allylic chloride **344** in the presence of a palladium catalyst afforded *(E)*-trisubstituted α,β-unsaturated ester **345** (Scheme 88).[118] Alternatively, β-stannyl ester **344** has been employed for the synthesis of a range of *(R)*-amino ester derivatives **345** in good yield.[119]



Scheme 88

Consequently the stereoselective preparation of α- or β-substituted esters has been widely investigated. For example, Piers *et al.* have reported that treatment of acetylenic esters **346** with stannyl cuprate reagents afforded *(E)*-3-trimethylstannylalkenoate **347** as the sole isomers (Scheme 89, Table 15).[120]



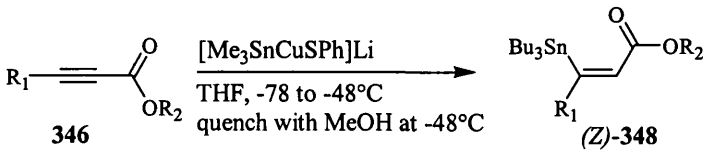
Scheme 89

	R_1	R_2	Yield (%)	*E:Z*[a]
1	Me	Et	76	> 95:5
2	^{i}Pr	Me	77	> 95:5
3	$Br(CH_2)_4$	Me	84	> 95:5
4	^{t}BuMe$_2$SiOCH$_2$	Et	80	95:5

[a] product ratios are determined by GLC analyses.

Table 15

Remarkably a reversal in *E:Z* stereoselectivity was observed if this reaction was allowed to warm up to –48°C prior to hydrolytic work-up. This variation of the procedure afforded in a stereoselective fashion the corresponding alkenoates *(Z)*-**348** (Scheme 90, Table 16).



Scheme 90

	R_1	R_2	Yield (%)	*Z:E*
1	Me	Et	78	> 1:99[a]
2	Me	Et	76	98:2[b]
3	^{t}Bu	Et	86	98:2
4	^{t}BuMe$_2$SiO(CH$_2$)$_2$	Me	81	96:4
5	$Br(CH_2)_4$	Me	74	95:5

[a] The reaction is quenched at –78°C; [b] The reaction is quenched at –48°C.

Table 16

Piers proposed that the trimethylstannane copper(I) reagent initially adds *syn* to the triple bond to form intermediate **349**, which on hydrolysis at –78°C afforded *(E)*-3-trimethylstannyl-2-alkenoates **347**. On warming to –48°C adduct **349** isomerised to the thermodynamically more stable allenoate **320** which on hydrolysis was protonated to afford *(Z)*-**348** (Figure 23).

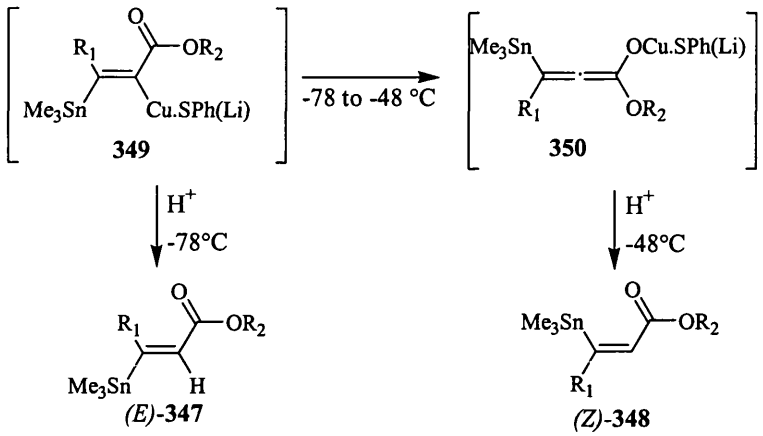
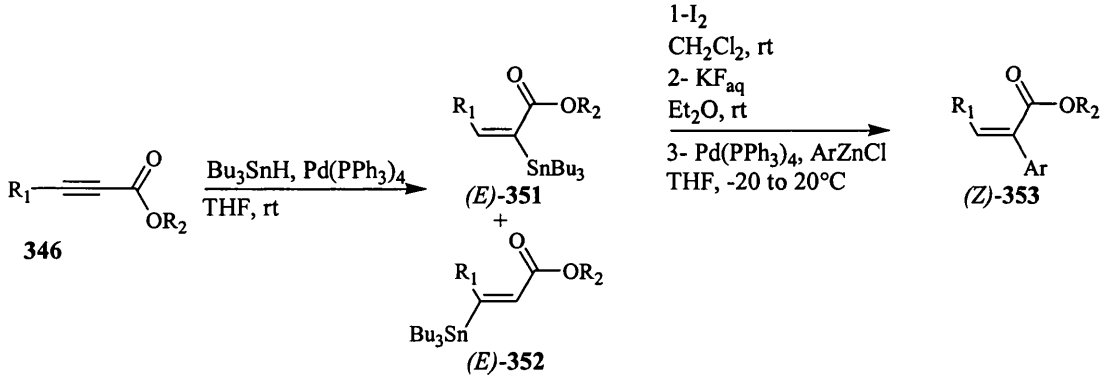


Figure 23

Rossi *et al.* have reported an elegant alternative stereo and regioselective preparation of α-aryl-2-alkenoate *(Z)*-**353**.[121] The reaction of acetylenic esters **346** with tributylstannane reagent in the presence of a palladium catalyst afforded *(E)*-tributylstannyl-2-alkenoates **351** in a regioselective and stereoselective fashion. Instead of employing a direct Stille coupling, *(E)*-**351** was converted to their 2-aryl-α,β-unsaturated esters *(Z)*-**353** *via* substitution of the stannyl group with iodide, and cross-coupling with organozinc reagents (Scheme 91, Table 17).



Scheme 91

	R_1	R_2	Yield (%)	351:352	*E:Z*
1	$^{n}C_5H_{11}$	Me	85	92:8	98:2
2	Ph	Et	71	90:10	99:1
3	$^{t}BuMe_2SiOCH_2$	Et	84	91:9	99:1
4	*(S)*-^{i}Bu	Et	93	98:2	>99:1

Table 17

2.2.5 Lithium ynolates

In the past twenty years several methods for the generation of ynolates or ketene anions have been developed, making them more synthetically accessible thus, allowing the study of their reactivity.[122] In 1982, Kowalski *et al.* observed that when α-bromo lithium enolate anion **354** was treated with base, rearrangement afforded ynolate anion **355**.[123] This reaction is an analogue of the Hofmann rearrangement where *N*-bromoamide **356** is deprotonated with sodium hydroxide followed by migration of the alkyl substituent R to nitrogen with loss of bromide to afford isocyanate **357** (Figure 24).[124]

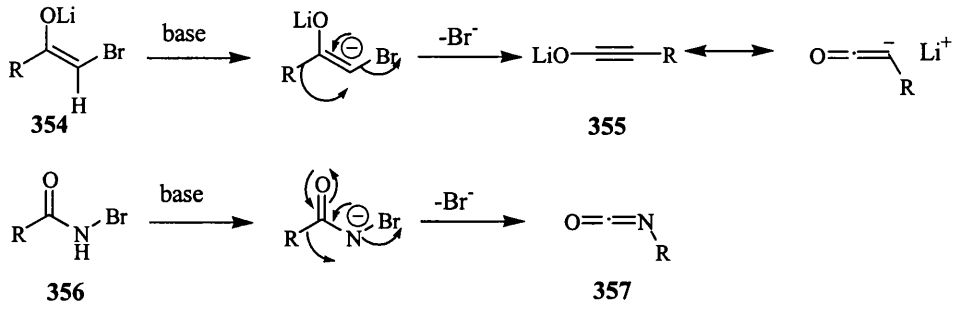
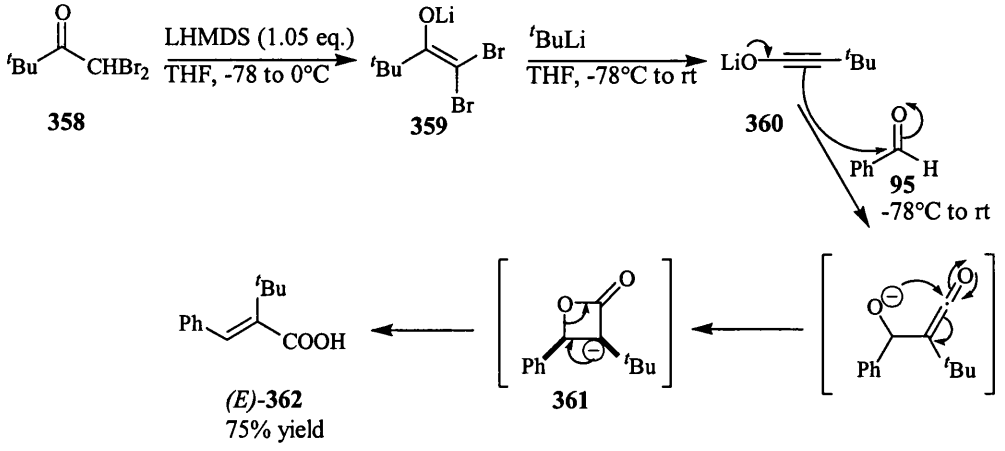


Figure 24

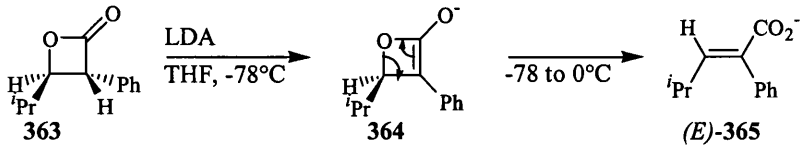
For example, dibromoketone **358** was deprotonated by action of LHMDS to afford dibromoenolate **359**, which on addition of ᵗbutyl lithium underwent an elimination/migration reaction to afford lithium ynolate **360**. Alkynolate **360** underwent subsequent nucleophilic addition to benzaldehyde **95** to yield *(E)*-α,β-unsaturated carboxylic acid **362**. Kowalski proposed that the key reaction that determines *(E)*-selectivity occurred *via* elimination of CO_2 from a β-lactone intermediate **361** (Scheme 92).



Scheme 92

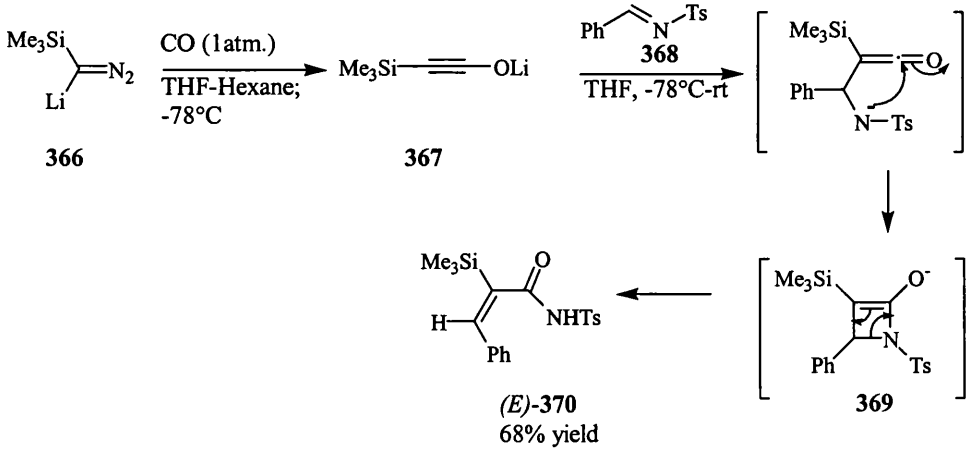
Mulzer *et al.* previously reported that treatment of β-lactone **363** with LDA produced an enolate **364** that was stable at –78°C.[125] On warming to room temperature the expected

β-elimination reaction occurred and the acrylic acid *(E)*-**365** was formed in quantitative yield, thus supporting the 4-membered intermediate **361** that Kowalski had proposed to explain the outcome of the addition of ynolates to aldehydes (Scheme 93).



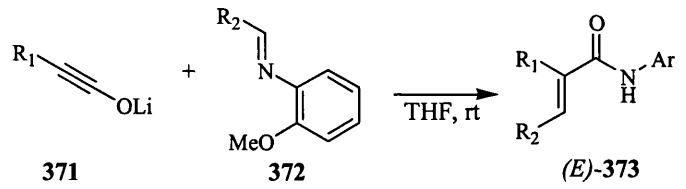
Scheme 93

Murai *et al.* became interested in this type of ketenylation reaction 15 years later and designed an efficient procedure to convert lithiosilyldiazomethane **366** into lithium silyl ynolate **367** under one atmosphere of carbon monoxide and reported its reactivity towards a number of electrophilic substrates such as epoxides or aldimines.[126] For example, lithium ynolate **367** reacted with aldimine **368** to afford amide *(E)*-**370** as the sole geometric isomer, whereby the stereochemistry was explained *via* rearrangement to the β-lactam enolate **369** and subsequent ring-opening (Scheme 94).



Scheme 94

Shindo *et al.* subsequently reported that this reaction showed good versatility for the reaction of a range of ynolates **371** and aldimines **372** affording *(E)*-unsaturated esters **373** with excellent selectivities (entries 1-3).[127] However, this reaction did suffer from some limitations; imines containing electron-withdrawing aromatic ring did not react (entry 4) whilst neither did bulky lithium ynolate (entry 5) (Scheme 95, Table 18).



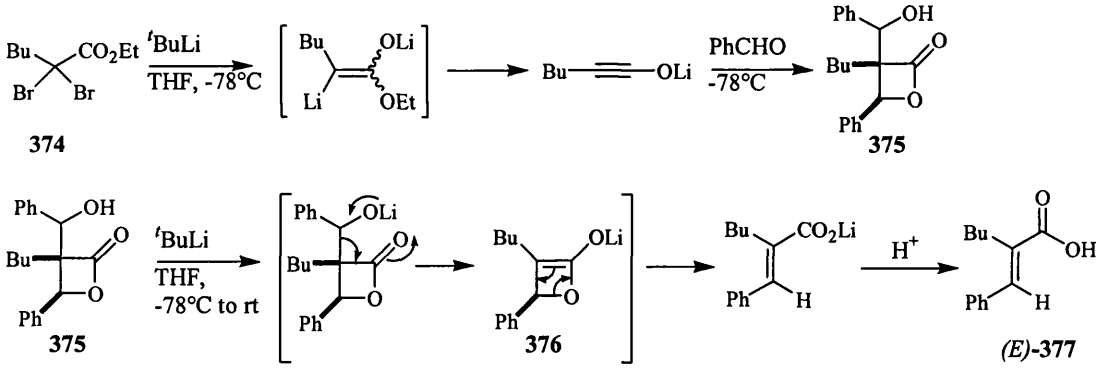
371 372 *(E)*-373

Scheme 95

	R_1	R_2	%Yield	*E:Z*
1	Me	Phenyl	88	>99:1
2	Me	^{t}Bu	52	>99:1
3	Cyclohexyl	phenyl	83	85:15
4	Me	4-(MeO_2C)C_6H_5	0	-
5	^{t}Bu	phenyl	0	-

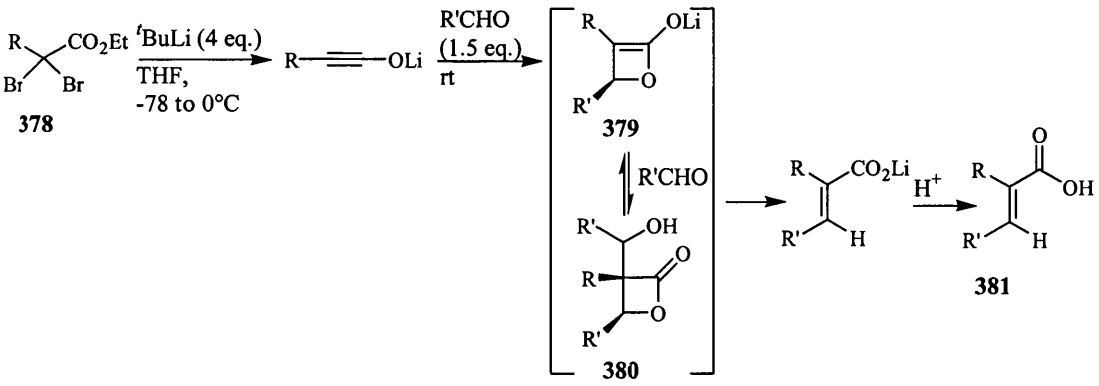
Table 18

Shindo *et al.* have reported that treatment of dibromoester **374** with two equivalents of ^{t}BuLi and two equivalents of aldehyde gave a trisubstituted β-lactone **375**.[128] They reported that further treatment of this lactone **375** with an extra equivalent of ^{t}BuLi resulted in formation of an unsaturated carboxylic acid *(E)*-**377** *via* a tandem *retro*-aldol reaction, followed by ring-opening of a cyclobutene enolate intermediate **376** (Scheme 96).[129]



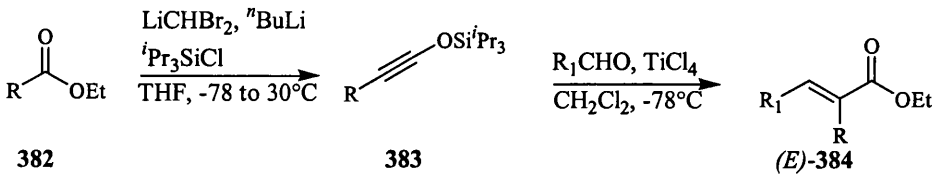
Scheme 96

Shindo has reported a related one-pot modification of this synthesis in which treatment of dibromoketone **378** with base, followed by addition of an excess of benzaldehyde yielded a mixture of lactones **379** and **380** that collapsed in a stereoselective manner to afford *(E)*-acid **381** (Scheme 97).



Scheme 97

Finally, Kowalski *et al.* proposed a *novel* olefination procedure to prepare *(E)*-trisubstituted unsaturated esters in two steps.[130] They reported the formation of silyloxyacetylene **383** from ethyl ester **382**, which was subsequently reacted with a range of aldehydes with good *(E)*-stereocontrol to afford *(E)*-**384** in good d.e. (Scheme 98, Table 19).



Scheme 98

	R	R_1	% yield	*E:Z*
1	C_5H_{11}	$(CH_2)_2Ph$	65	> 95:5
2	C_5H_{11}	Ph	64	84:16
3	Ph	C_5H_{11}	65	> 95:5
4	C_6H_{11}	$(CH_2)_2Ph$	63	> 95:5

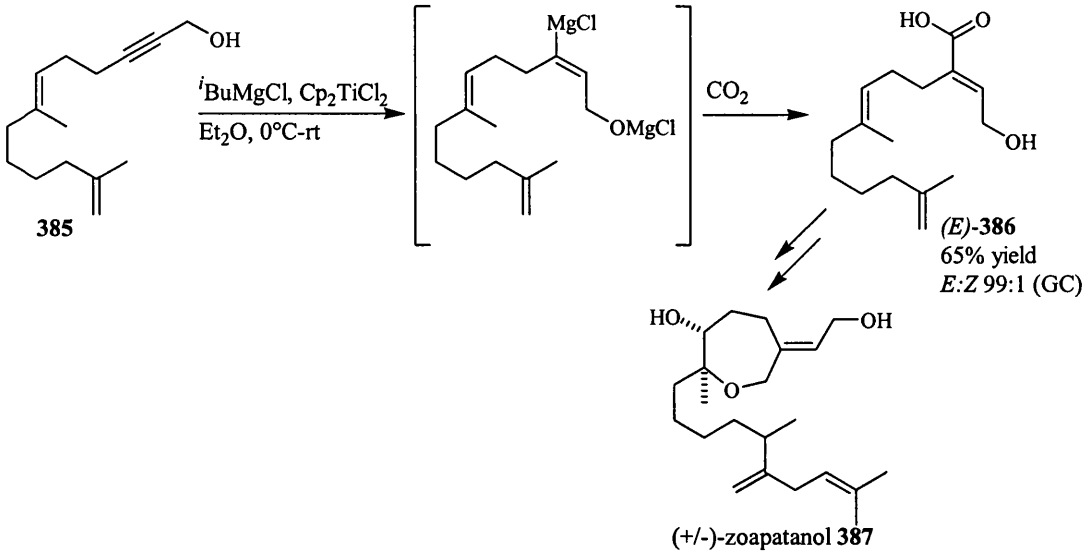
Table 19

2.2.6 Miscellaneous

2.2.6.1 Hydrocarboxylation of alkynes

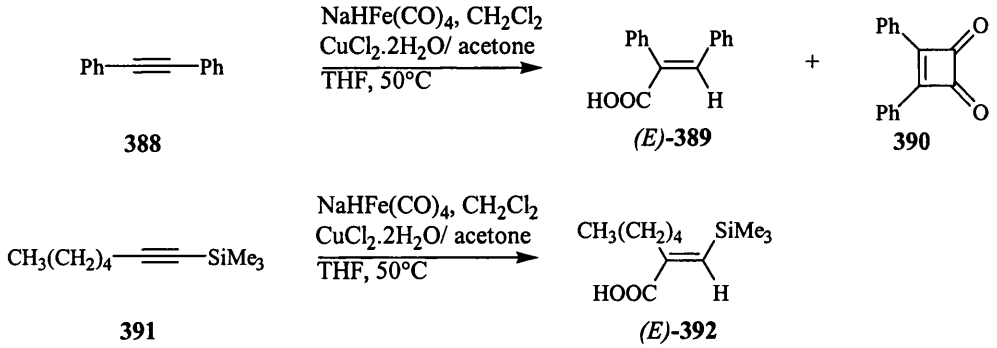
Hydrocarboxylation of acetylene is a major industrial process for the large scale production of acrylic acid derivatives, however, hydrocarboxylation of unsymmetrical alkynes often affords mixtures of geometric stereoisomers.[131] Kocienski *et al.* have reported the use of this type of methodology for the stereoselective synthesis of anti-fertility agent zoapatanol **387**.[132] In order to achieve selective carboxylation, alkyne **385** was subjected to addition of Grignard reagent ^{i}BuMgCl in the presence of Cp_2TiCl_2 to afford after quenching with

carbon dioxide *(E)*-α-substituted-α,β-unsaturated carboxylic acid **386** in modest yield and in a regio and diastereoselective fashion (Scheme 99).



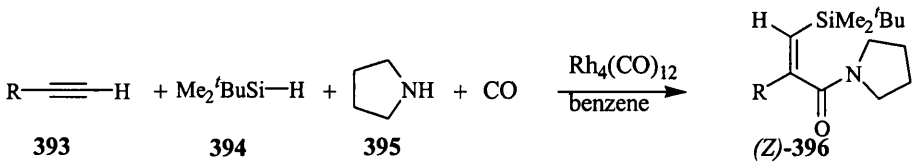
Scheme 99

An original approach to this chemistry was proposed by Periasamy *et al.* who reported on the regio and stereoselective synthesis of α,β-unsaturated carboxylic acid **389** and **392**.[133] Reaction of alkyne **388** with $NaHFe(CO)_4$ and CH_2Cl_2 in THF afforded a metal carbonyl complex that decomposed to give a 3:1 mixture of α,β-unsaturated carboxylic acid *(E)*-**389** and cyclobutenedione **390**. Under these conditions, alkyne **391** afforded α,β-unsaturated carboxylic acid *(E)*-**392** as the sole product in > 95% d.e. (Scheme 100). No intermediate or mechanism has yet been proposed for this reaction although an excess of CH_2Cl_2 was essential to optimise conversion since low yields were obtained in its absence.



Scheme 100

Matsuda *et al.* have reported on a one-pot procedure to condense an alkyne **393**, hydrosilane **394**, amine **395** and carbon monoxide in the presence of a rhodium Rh(0) catalyst, to afford *(Z)*-α,β-unsaturated amides **396** in good d.e. (Scheme 101, Table 20).[134]

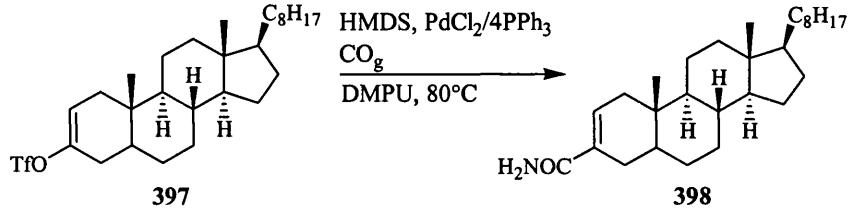


Scheme 101

	R	Yield (%)	*Z:E*
1	^{n}pentyl	82	96:4
2	cyclohexyl	73	96:4
3	phenyl	44	100:0

Table 20

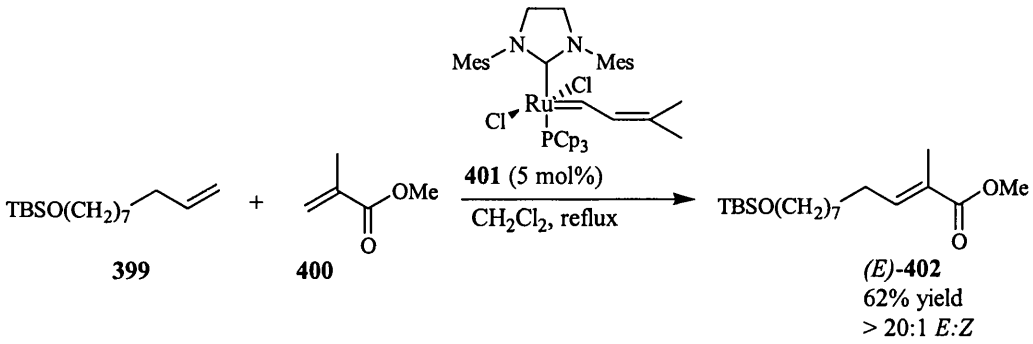
A related route towards trisubstituted α,β-unsaturated carboxylic acid has been described involving Pd(0) mediated carbonylation of alkenes that are substituted with halide or triflate substituents. For example, in 1998, Ortar *et al.* reported the preparation of primary *(E)*-amides and applied this approach to the synthesis of cholest-2-en-yl amide **398**.[135] Thus, vinyl triflate **397** was treated with HMDS and a catalytic amount of $PdCl_2/4PPh_3$ under a CO atmosphere to afford trisubstituted α,β-unsaturated amide **398** in excellent yield (Scheme 102).



Scheme 102

2.2.6.2 Cross metatheses

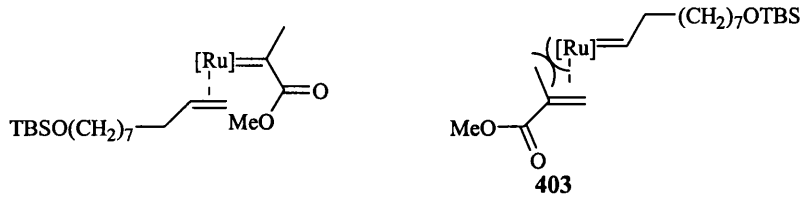
Grubbs *et al.* described a new route towards the synthesis of trisubstituted electron-poor alkenes, using their powerful ring-closing metathesis procedure to form the alkene functionality.[136] Thus, terminal olefin **399** participated in cross-metatheses reaction with methyl methacrylate **400** in the presence of ruthenium catalyst **401** to generate the trisubstituted unsaturated ester **402** in moderate yield but with excellent stereoselectivity (Scheme 103).



399 400 (E)-402
62% yield
> 20:1 E:Z

Scheme 103

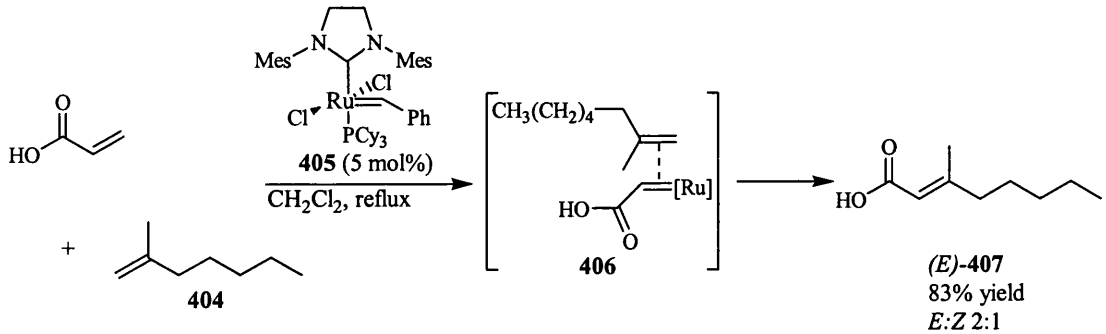
It was known that ester-α-carbene complexes were highly unstable, whilst α-substitution of the ester would hinder the approach of the ruthenium catalyst. Therefore Grubbs proposed that the *(E)*-trisubstituted ester formed in this reaction was derived from the ruthenium-terminal olefin complex **403** (Figure 25).



403

Figure 25

Grubbs *et al.* proposed though that changing the substitution pattern of the participating olefin fragments might also change the course of the metathesis reaction.[137] Indeed, substitution of a disubstituted olefin **404** hindered its complexation to the ruthenium catalyst **401**, which made formation of acid-carbene complex **406** more kinetically favoured. Thus, the reaction afforded the β-isomer *(E)*-**403** in good yield but with only modest diastereoselectivity (Scheme 104).



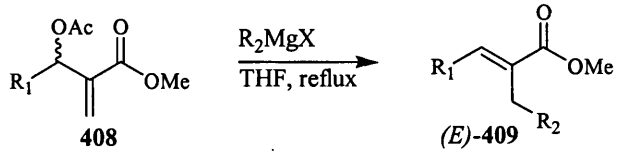
404 406 (E)-407
83% yield
E:Z 2:1

Scheme 104

2.2.6.3 Addition of carbanions to Baylis-Hillman adducts

In section 2.2.3.1 it was described how the reductive elimination of a Baylis-Hillman adduct affords α-methyl cinnamate esters, however Basavaiah *et al.* have reported an

alternative strategy whereby addition of a Grignard reagent to an allylic acetate offered wide versatility for substitution at the α-position.[138] For example, Baylis-Hillman adduct **408** reacted with a range of Grignard reagents to afford *(E)*-α-substituted alkenoates **409** as the sole isomers (Scheme 105, Table 21).



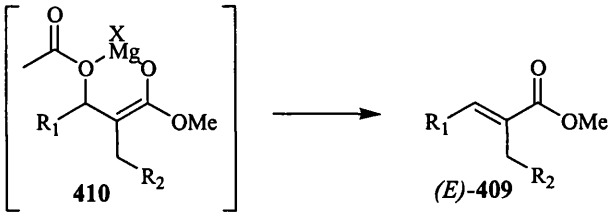
408 *(E)*-**409**

Scheme 105

	R_1	R_2	Yield (%)
1	Me	Ph	75
2	$^nC_6H_{13}$	^{n}Bu	62
3	Ph	^{n}Bu	70

Table 21

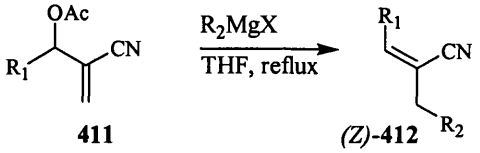
The *(E)*-selectivity was rationalised by invoking a chelated structure **410** in which the magnesium cation forms a six-membered ring, which collapses to afford the *(E)*-isomer **409** stereoselectively (Figure 26).



410 *(E)*-**409**

Figure 26

This rationale was supported by the observation that the addition of Grignard reagents to nitriles **411** under the same conditions was *(Z)*-selective. Thus, the addition of Grignard reagents to 3-acetoxy-2-methylenealkanenitrile **411** under the same reaction conditions afforded 2-substituted alk-2-ene nitriles *(Z)*-**412** as the major isomers in fair to good d.e. (Scheme 106, Table 22).



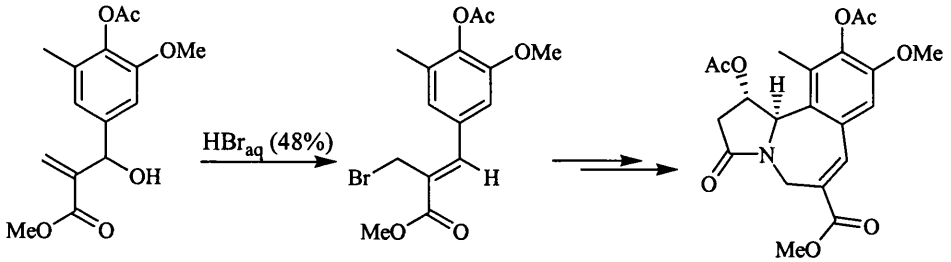
411 *(Z)*-**412**

Scheme 106

	R_1	R_2	Yield (%)	*Z:E*
1	^{n}Bu	^{n}Bu	73	82:18
2	Ph	Me	75	80:20
3	Ph	*p*-MeOPh	81	> 95:5

Table 22

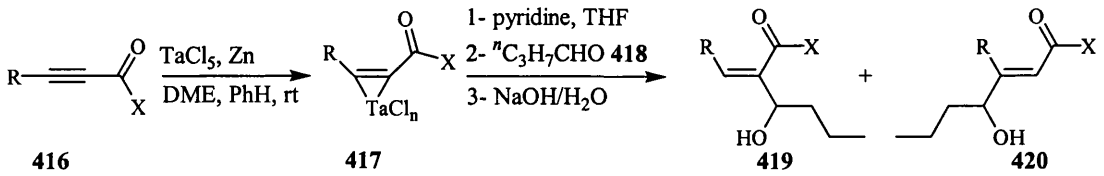
Marson *et al.* have reported the use of a variant of this procedure for the synthesis of aza analogues **415** of the ABC ring system of phorbol, *via* treatment of allylic alcohol **413** with HBr_{aq} to afford allylic bromide **414** (Scheme 107).[139]



Scheme 107

2.2.6.4 Metal insertion into alkynes

Takai, Utimoto *et al.* have reported on the insertion of an aldehyde **418** into a tantalum-carbon bond in a regioselective manner to afford Baylis-Hillman-like α-substituted α,β-unsaturated esters *(Z)*-**419** *via* intermediate **417** (Scheme 108, Table 23).[140] Electronic effects appear to control the α,β-regioselectivity for ethyl esters (entries 1-3) with the ester substituent polarising the alkene to favour the formation of intermediate **421**, with alkaline hydrolysis of **421** subsequently affording the desired trisubstituted unsaturated ester **419**.



Scheme 108

	R	X	Yield (%)	419:420
1	^{n}C$_{10}$H$_{21}$	OEt	76	95:5
2	C$_6$H$_{11}$	OEt	76	98:2
3	Ph	OEt	57	91:9
4	^{n}C$_6$H$_{13}$	NMe$_2$	79[a]	10:90

[a] The reaction was carried out at 50°C.

Table 23

In contrast to acetylenic esters, reaction of a tantalum-acetylenic amide complex (entry 4) yielded predominantly the β-regioisomer **420**. It was shown that complexation of tantalum to electron-poor alkyne **416** proceeded exceptionally fast while the reactivity of the resultant complex **417** with butyraldehyde **418** was slower. β-Selectivity in this case was therefore attributed to coordination between the nitrogen lone pair of the amide fragment and low-valent tantalum, preferentially affording intermediate **422** (Figure 27).

Figure 27

CHAPTER 3. A *novel* Concept for the Asymmetric Synthesis of Aldehydes

The remainder of this thesis describes the discovery and development of synthetic methodology that employs *syn*-β-hydroxy-*N*-acyloxazolidin-2-ones as substrates for a *novel* intramolecular cyclisation/elimination reaction to afford trisubstituted *(E)*-α,β-unsaturated amides in high d.e. As is often the case, this *novel* methodology was discovered as part of another research program directed towards employing chiral auxiliaries for asymmetric synthesis in a *novel* manner using concepts that are still under active investigation within the SDB research group. Consequently, I will first discuss this original chiral auxiliary concept, and the preliminary reactions that were carried out that led to the discovery of this *novel* methodology for the stereoselective synthesis of *(E)*-trisubstituted acid derivatives.

3.1 A new concept for using chiral auxiliaries for asymmetric synthesis

3.1.1 The use of chiral auxiliaries for asymmetric synthesis

To recap, chiral auxiliaries are widely used in asymmetric synthesis for the stereoselective synthesis of a wide range of enantiopure compounds. Conventional chiral auxiliaries operate according to a general strategy in which a chiral auxiliary fragment **CA** is covalently attached to a prochiral substrate **S** to afford a covalent complex **CA-S**; which is then transformed stereoselectively (under the control of the chiral auxiliary fragment **CA**) to afford a new product **CA-P** which contains one or more new stereocentres (**NS**). The product **CA-P** is then cleaved to afford an enantiopure product **P** and the chiral auxiliary **CA** which is then recycled as required (Figure 28).

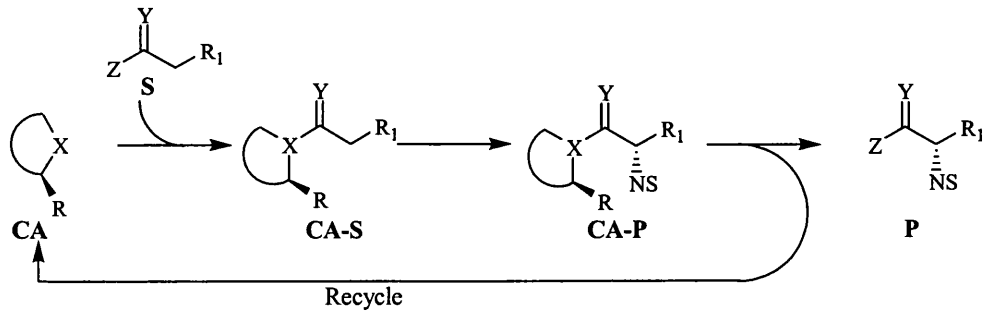
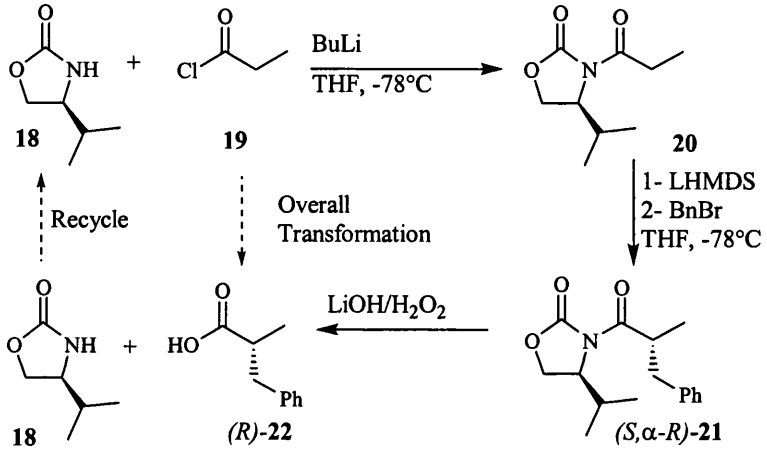


Figure 28

Perhaps the most widely used chiral auxiliaries to date are chiral oxazolidin-2-ones such as *(S)*-**18** described originally by Evans *et al.* which have been used for stereocontrol in a wide range of reaction scenarios including asymmetric aldol reactions,[141] conjugate additions,[142] and Diels-Alder reactions.[143] For example, Evans' oxazolidin-2-one was used as a chiral auxiliary for the asymmetric synthesis of chiral acid fragments according to the enolate alkylation protocol described in Scheme 109. Thus, the chiral oxazolidin-2-one *(S)*-**18** was attached to an achiral acyl chloride fragment **19** to afford *N*-acyl-oxazolidin-2-one **20**, which was deprotonated with LHMDS to afford a lithium *(Z)*-enolate that reacted with electrophiles such as benzyl bromide to afford an α-benzylated-*N*-acyl-oxazolidin-2-one *(S,α-R)*-**21** in high d.e. Subsequent hydrolysis of *(S,α-R)*-**21** then afforded the desired chiral acid *(R)*-**22** in enantiopure form, and the chiral auxiliary fragment **18** which could be recycled as required.[10]



Scheme 109

3.1.2 A new approach to the use of chiral auxiliaries

An alternative strategy for using chiral auxiliaries in asymmetric synthesis may be proposed, in which the chiral auxiliary fragment **CA** reacts with the achiral functionality ($\mathbf{A_1}$) of a substrate **S** to afford a complex **CA-S** that contains a new 'temporary' stereogenic centre ($\mathbf{TS_1}$). The newly formed temporary stereocentre ($\mathbf{TS_1}$) of **CA-S** may then be employed to subsequently control facial selectivity during stereoselective transformation of prochiral functionality $\mathbf{A_2}$ (contained within **CA-S**), to afford a transformed product **CA-P** containing a second new stereogenic centre ($\mathbf{NS_2}$). Subsequent cleavage of product **CA-P** would result in destruction of the temporary stereocentre $\mathbf{TS_1}$ (regenerating achiral functionality $\mathbf{A_1}$) to afford a product **P** containing a new stereocentre $\mathbf{NS_2}$, and the chiral auxiliary fragment **CA**, which could then be recycled as required (Figure 30).

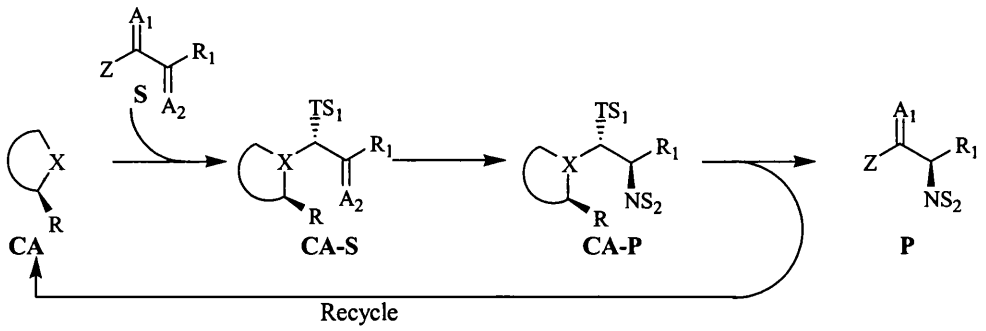


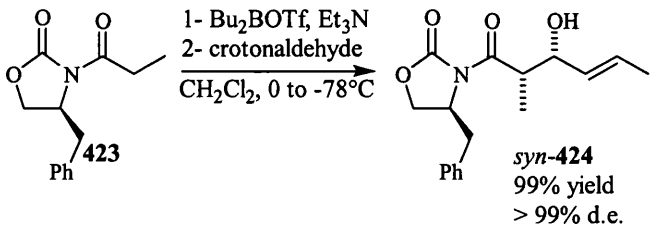
Figure 30

Clearly, for this *novel* approach towards chiral auxiliary use to be successful it required that the newly formed 'temporary' stereocentre (TS_1) of **CA-S** should contain functionality that was capable of carrying out directed stereoselective transformations. It was well known that stereogenic hydroxyl groups have the capacity to carry out directed chemical reactions for a wide range of stereoselective transformations in high d.e. (see section 1.6) Given the capacity of the aldol/*retro*-aldol reaction to form/cleave stereodefined β-hydroxy-aldolate fragments, it was proposed that this combination of synthetic transformations would be ideally suited for the design of this new class of chiral auxiliary.

3.1.3 Evans' *N*-acyl-oxazolidin-2-ones as a prospective chiral auxiliary fragment

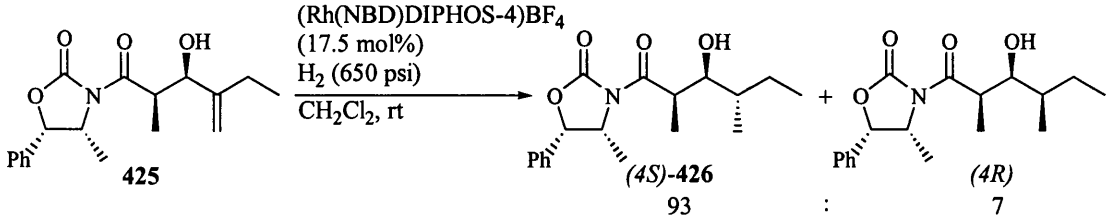
In order to develop a working model of the novel chiral auxiliary concept described in Figure 30, we required a chiral auxiliary fragment that would not only afford aldolates in high d.e., but that would also afford aldolates that underwent *retro*-aldol reaction under controlled conditions.

An extensive review of the literature revealed that a working system based on the use of chiral Evans' *N*-acyl-oxazolidin-2-ones might be ideally suited to these purposes. Firstly, boron enolates of *N*-acyloxazolidin-2-ones were well known to undergo stereoselective aldol reactions with a wide range of aldehydes. For example, aldol reaction between the boron enolate of *N*-propionyl-*(4S)*-benzyl-oxazolidin-2-one **423** and crotonaldehyde was known to afford quantitatively a *syn*-aldolate **424** in > 99% d.e. (Scheme 110).[144]



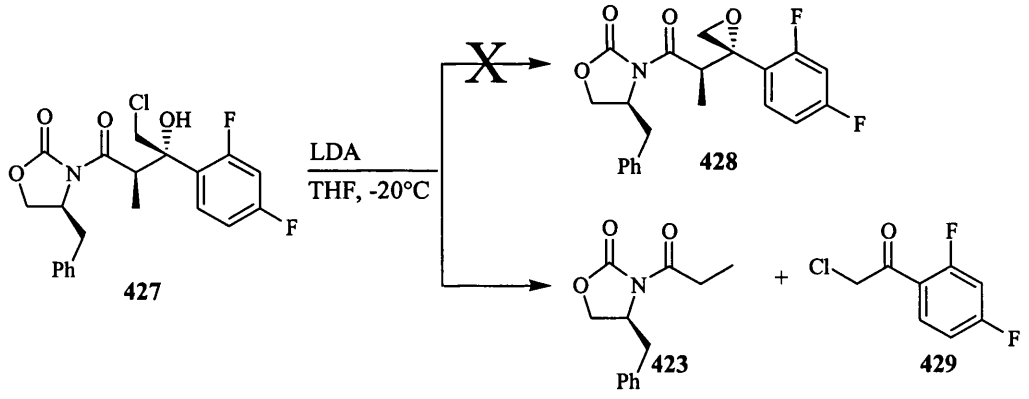
Scheme 110

Secondly, it was well established that directed hydrogenation reactions of chiral allylic alcohols in the presence of certain transition metal catalysts occurred in a highly stereoselective manner to afford chiral alcohols that contained new stereogenic centres in high d.e.[5] More specifically, Evans *et al.* had reported that directed hydrogenation of the chiral allylic alcohol functionality of *N*-acyl-oxazolidin-2-one **425** afforded a saturated alcohol *(4S)*-**426** product in high d.e., where hydrogen had been delivered to the alkene functionality from the same face as the β-hydroxyl group (Scheme 111).[145]



Scheme 111

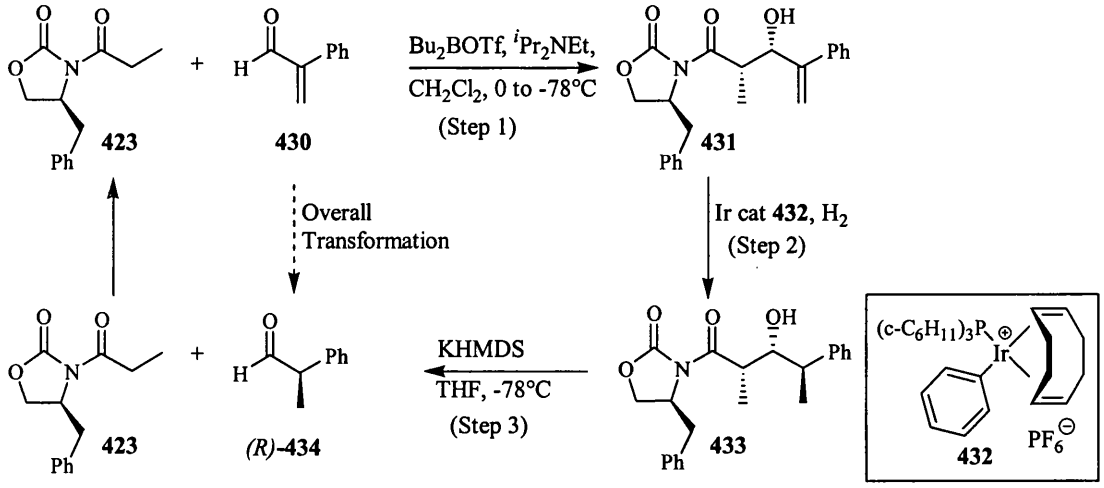
Thirdly, a survey of the literature revealed that a single example of a base-promoted *retro*-aldol cleavage of a β-hydroxy-*N*-acyl-oxazolidin-2-one had already been reported. Thus, Bartroli *et al.* demonstrated that kinetic deprotonation of the hydroxyl functionality of ketolate **427** with LDA at -40°C did not afford the desired epoxide **428** as expected, but instead underwent clean *retro*-aldol fragmentation to afford the parent *N*-acyl-oxazolidin-2-one **423** and α-chloro-ketone **429** (Scheme **112**).[146]



Scheme 112

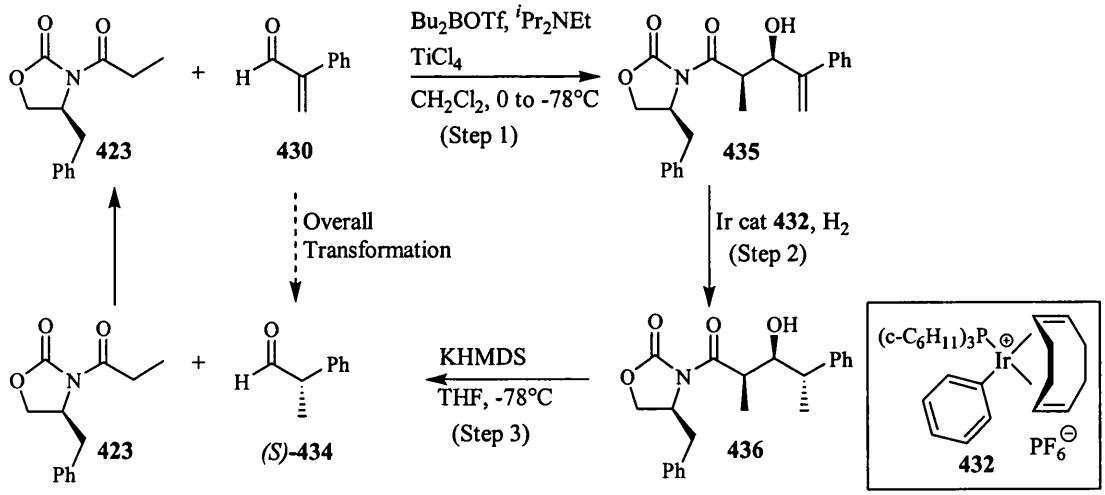
It was proposed that combining these three literature precedents would enable us to realise the *novel* concept for using chiral auxiliaries for asymmetric synthesis as described in Scheme 113. Thus, reaction of the boron enolate of *N*-propionyl-2-oxazolidin-2-one **423** with 2-phenyl propenal **430** would afford *syn*-aldolate **431** (step 1); directed hydrogenation of *syn*-aldolate **431** with Crabtree's catalyst **432** under the control of the stereogenic hydroxyl group would afford *syn*-aldolate **433** containing a new stereocentre (step 2);[147] *retro*-aldol reaction of aldolate **433** would afford *(S)*-2-phenyl-propionaldehyde **434**, and

the chiral auxiliary fragment **423** which could be recycled as required. This protocol would therefore result in an overall transformation in which the achiral α,β-unsaturated aldehyde **430** had been stereoselectively hydrogenated to afford chiral aldehyde *(R)*-**434** that contained a new stereocentre at its α-position.



Scheme 113

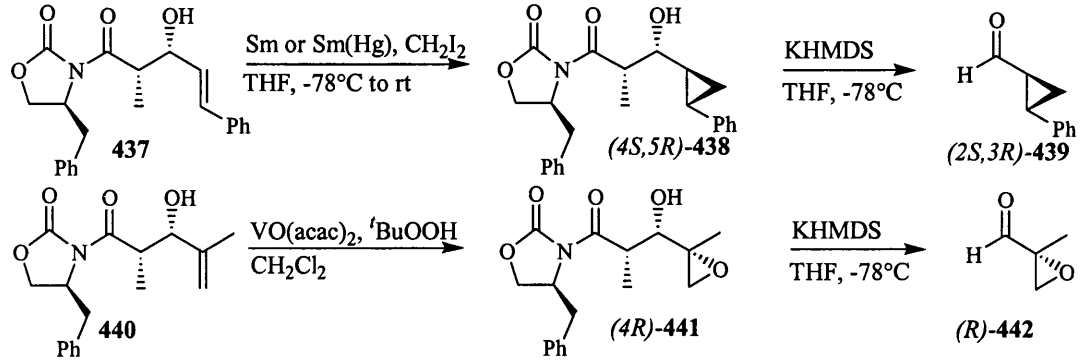
Alternatively, it was proposed that the readily available *syn*-aldolate product **435** could also be subjected to the same type of hydrogenation/*retro*-aldol protocol to afford the corresponding *(S)*-α-methyl aldehyde **434** (Scheme 114), thus enabling the same enantiomer of *(S)*-4-benzyl-*N*-propionyloxazolidin-2-one **423** to be employed for the preparation of either enantiomer of 2-phenylpropionaldehyde *via* a stereodivergent approach (Scheme 114).



Scheme 114

Once the aldol/directed hydrogenation/*retro*-aldol methodology described had been optimised then it was my intention to further explore the capacity of the β-hydroxyl functionality of aldolates such as **437** and **440** to control other directed stereoselective

transformations such as cyclopropanations,[19] or epoxidations.[11,12,13] These reactions would result in aldolate products **438** and **441** that could potentially undergo *retro*-aldol reactions to afford chiral aldehyde products such as **439** and **442** that contain cyclopropyl or epoxide functionality respectively (Scheme 115).



Scheme 115

It was reasoned therefore that applying this type of aldol/directed reaction/*retro*-aldol strategy to a wide range of aldolate substrate, for a range of different types of hydroxyl directed reaction, would enable the development of versatile methodology for the asymmetric synthesis of libraries of chiral aldehyde fragments that contained a diverse range of functionality. It should be noted that there are currently few methods available for the direct asymmetric synthesis of chiral aldehyde fragments, which are a class of compound that are highly prized in synthesis.

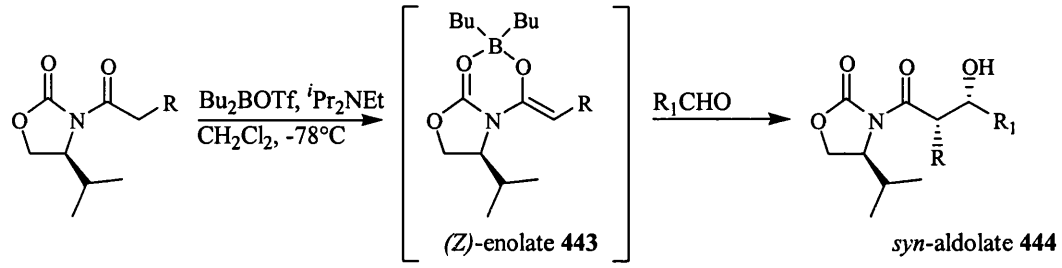
3.2 Development of an effective *syn*-aldol reaction using boron enolates of *N*-acyl-oxazolidin-2-ones

My first goal was to develop an effective and robust protocol for carrying out stereoselective reactions between boron enolates of *N*-acyloxazolidin-2-one and α,β-unsaturated aldehydes to afford *syn*-aldolates in high d.e. A great deal of literature precedent exists for this type of *syn*-selective aldol reaction and relevant reports will now be discussed in brief.

3.2.1 Literature precedent

(Z)-Enolates derived from *N*-acyl-oxazolidin-2-ones have been widely employed for the asymmetric synthesis of enantiopure aldolate products containing a diverse range of functionality in high d.e. Pioneering work carried out by Evans *et al.* resulted in the development of methodology that enables the stereoselective formation of *syn*-aldolate fragments.[148] Thus, while lithium enolates of *N*-acyl-oxazolidin-2-ones generally exhibit

low levels of control in aldol reactions, the corresponding boron *(Z)*-enolates **443** afford remarkably high stereochemical control for kinetic aldol reactions with a wide range of aldehydes to afford *syn*-aldolates **444** in high d.e (Scheme 116).



Scheme 116

The stereochemistry of the resulting *syn*-aldolate product **444** may be rationalised by invoking a boron chelated chair transition state in which the R_1 substituent of the aldehyde substrate prefers to occupy an equatorial environment. Consideration of the relative energies of the chelated chair transition states S_1 and S_2 revealed that formation of 'Non-Evans' *syn*-aldolate **445** was disfavoured by steric interactions between the *iso*propyl stereodirecting group of the oxazolidin-2-one and the chelated boracycle fragment. Thus, the alternative 'Evans' *syn*-aldolate **444** was formed in high d.e. under these conditions (Figure 31).

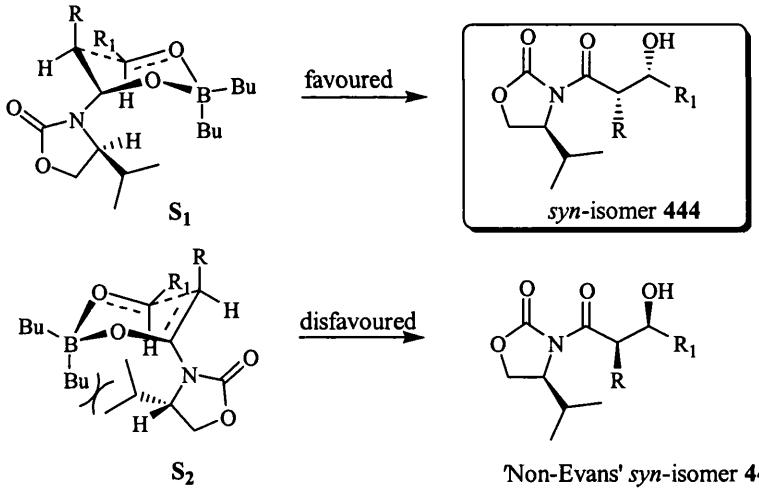
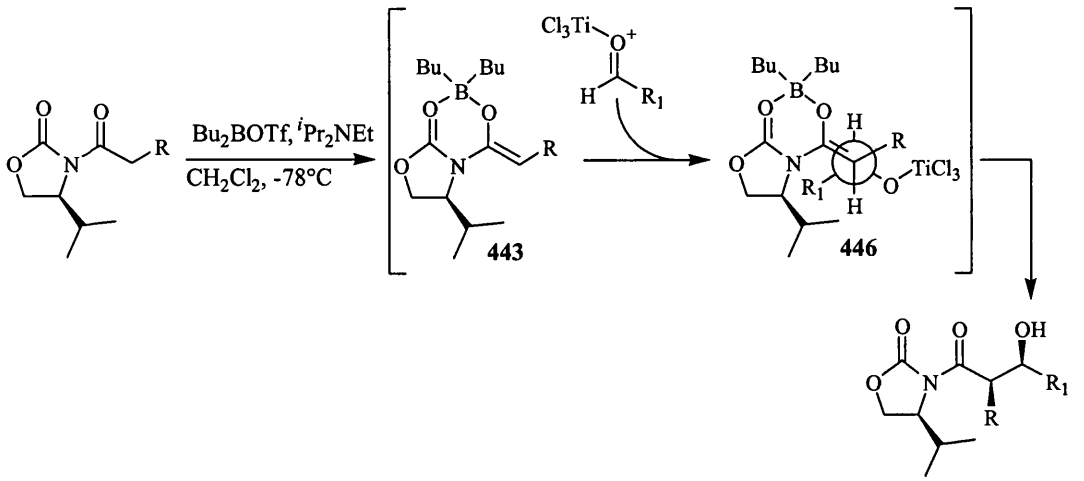


Figure 31

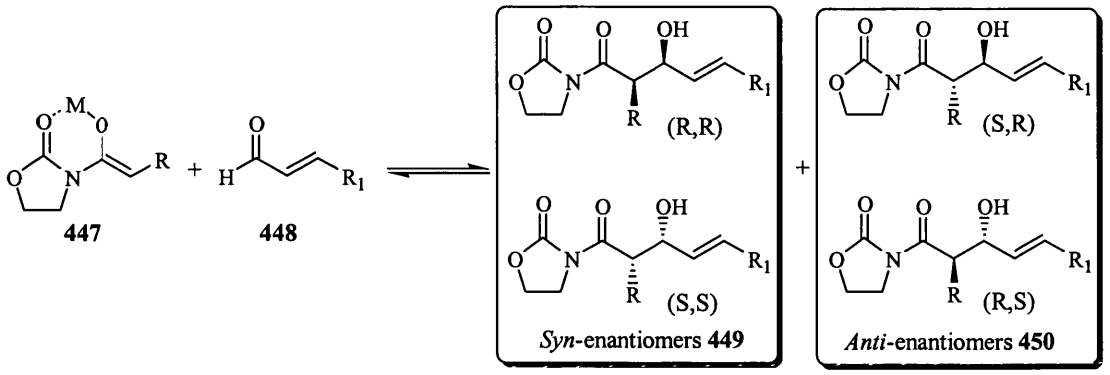
Heathcock *et al.* later introduced an alternative protocol for the formation of 'non-Evans' *syn*-aldolates **445** in high d.e. in which the aldehyde substrate was precomplexed to a strong Lewis acid $TiCl_4$ before addition to the boron enolate **443** in the usual manner.[149] It was proposed that this aldol reaction proceeded *via* an 'open' transition state **446** in which steric interactions between the R-alkyl group of the *(Z)*-enolate **443** and the R_1 alkyl group of the aldehyde were minimised (Scheme 117).



Scheme 117

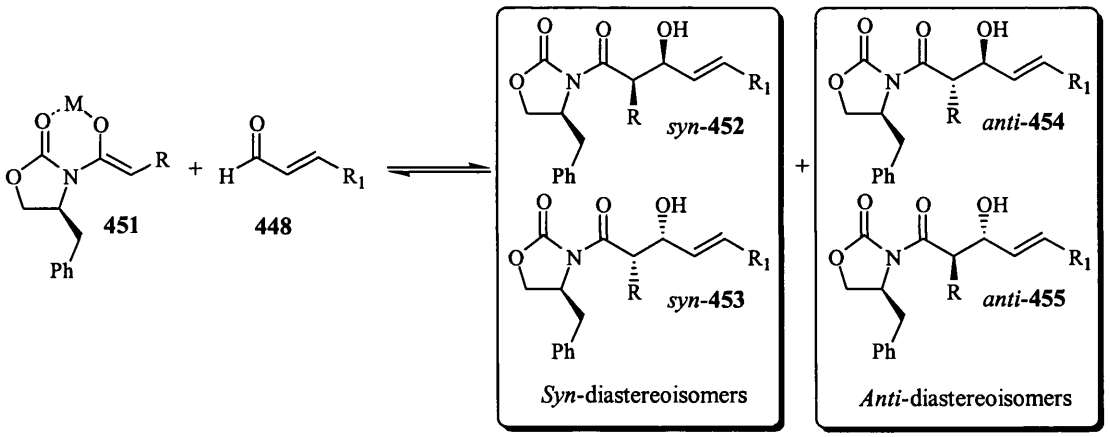
3.2.2 Achiral *N*-acyl-oxazolidin-2-ones as substrates for optimising *syn*-selective aldol reactions

As described, the synthesis of *syn*-aldolate products employing aldol reaction between *(Z)*-boron enolates of *N*-acyl-oxazolidin-2-ones and achiral aldehydes is well-established, with over 100 reports having been described to date on its use for stereoselective synthesis.[150] Despite this popularity however, it is well known within the synthetic community that this stereoselective aldol methodology can be highly capricious and that the yields and diastereoselectivities of aldolate products are highly dependent on the quality of the boron Lewis acid employed for reaction. In order to optimise the conditions employed for the aldol reactions I initially concentrated on the preparation of racemic *syn*-**449** aldolate products derived from condensation of the boron enolate of an *achiral N*-acyl-oxazolidin-2-one **447** with an α,β-unsaturated aldehyde **448**. The decision to carry out initial optimisation studies using this model system was taken in order to help simplify ^{1}H NMR spectroscopic analysis of crude product mixtures. Thus, for any 'unsuccessful' stereoselective aldol reaction carried out using the enolate of achiral *N*-acyl-oxazolidin-2-one **447**, only two new compounds *syn*-aldolate *(rac)*-**449** and *anti*-aldolate *(rac)*-**450** would be observed in the ^{1}H NMR spectrum of the crude reaction products (Scheme 118).



Scheme 118

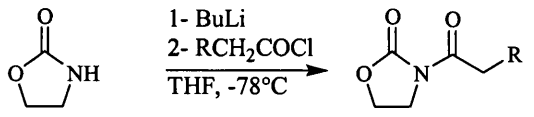
This simplicity compares with the potential difficulties in analysing the ^{1}H NMR spectrum of crude reaction products in which the enolate of a chiral *N*-acyl-oxazolidin-2-one such as **451** had been used for optimisation studies, where an 'unsuccessful' stereoselective aldol reaction would potentially afford four possible aldolate diastereoisomers products, *syn*-**452**, *syn*-**453**, *anti*-**454**, and *anti*-**455**, all of which would afford their own set of distinct signals in the ^{1}H NMR spectrum (Scheme 119).



Scheme 119

3.2.3 Preparation of achiral *N*-acyl-oxazolidin-2-ones

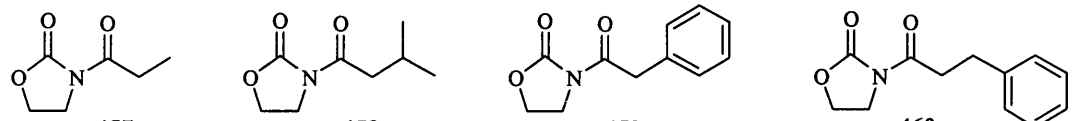
Therefore, my first synthetic target was to prepare a range of achiral *N*-acyl-oxazolidin-2-ones **457-460** (Scheme 120, Figure 32) as substrates for carrying out optimisation studies of the *syn*-selective aldol reaction. *N*-acyl-oxazolidin-2-ones **457-460** were prepared *via* treatment of the parent achiral oxazolidin-2-one **456** with ^{n}BuLi in THF at –78°C, followed by addition of the appropriate acid chloride and warming to room temperature.[151] Purification of the crystalline *N*-acyl-oxazolidin-2-ones was afforded in fair to good yield, *via* recrystallisation from ethyl acetate, or *via* chromatography over silica.



456 **457-460**

R = Me, ^{i}Pr, Ph, CH_2Ph

Scheme 120

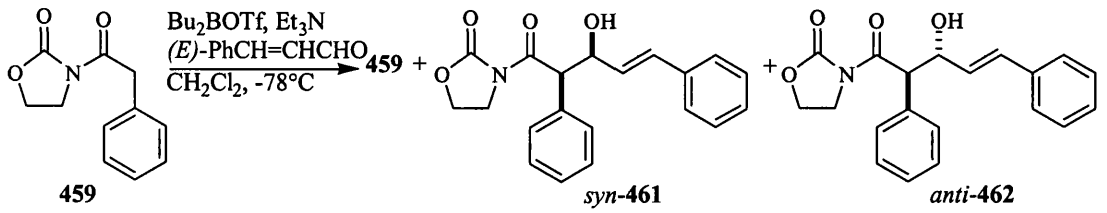


457 72% yield **458** 74% yield **459** 62% yield **460** 73% yield

Figure 32

3.2.4 S*yn*-aldol reactions using dialkylboron triflates as Lewis acids

Initially, the aldol reaction between achiral *N*-phenylacetyl-oxazolidin-2-one **459** and *trans*-cinnamaldehyde was investigated employing commercially available dibutylboron triflate (Aldrich, 1M in dichloromethane) as a stoichiometric Lewis acid, under the range of conditions described in Table 24. The overall yield of aldolate product formed in these reactions was disappointing however, with the best results being obtained using 1.5 equivalents of dibutylboron triflate in CH_2Cl_2 at 0°C, which afforded *syn*-**461** in only 38% yield after exhaustive chromatographic purification. Analysis of the ^{1}H NMR spectrum of this crude reaction mixture revealed that whilst *syn*-aldolate **461** had been formed in high d.e., the poor overall yield was a result of large amounts of unreacted starting material **459**. However, *syn*-aldolate **461** was fully characterised. The ^{1}H NMR spectrum revealed a strong coupling of J=7 Hz between α-C*H*Ph (5.24 ppm, d) and β-C*H*OH (4.95 ppm, app t). The infra-red spectrum of this compound showed two bands of absorption in the carbonyl region at 1694 and 1778 cm^{-1} whilst the correct molecular ion at 337 (M^{+}, CI^{+}) was also observed.



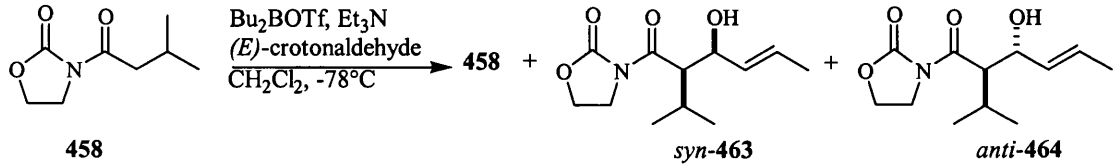
Scheme 121

Conditions. Ratio of **459** : Et_3N : Bu_2BOTf	Ratio **459** : *syn*-**461** : *anti*-**462**		
1.0: 1.2: 1.1	53	>45	<2
1.0: 1.6: 1.5	28	>68	<4
1.0: 2.1: 2	54	41	5

Ratios were calculated by measurement of the integrals in the ^1H NMR of the crude reaction mixture.

Table 24

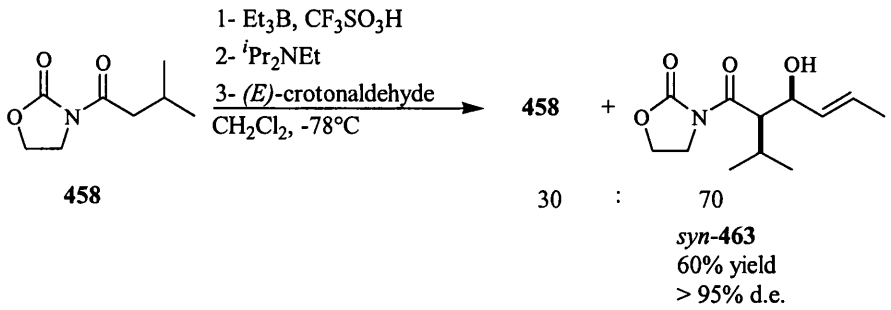
It was reasoned that the low yield of *syn*-aldolate product **461** observed in this aldol reaction might be a consequence of potential stability problems associated with *trans*-cinnamaldehyde (stabilised *via* conjugation to aryl ring), and with the enolate of *N*-phenylacetyl-oxazolidin-2-one **459** (stabilised by presence of α-phenyl substituent). As a consequence it was decided to carry out the aldol reaction using achiral *N*-acyl-oxazolidin-2-one **458** and *trans*-crotonaldehyde. However, under optimal conditions (Table 24, entry 2), only marginal improvement was observed with a disappointing 42% yield of the desired *syn*-aldolate product **463** being obtained after chromatographic purification.



Scheme 122

As indicated, it was well known that the quality of boron triflate reagent used for carrying out this type of *syn*-aldolate reaction was an important factor in the yield of aldolate product obtained. Consequently, it was decided to freshly prepare my own sample of Et_2BOTf for reaction, which would then be used immediately for a stereoselective *syn*-aldol reaction. Thus, a solution of Et_2BOTf in CH_2Cl_2 was prepared by addition of triflic acid to triethylborane, warming to 40°C, followed by cooling to –78°C. This solution of boron reagent was then transferred to a solution of *N*-acyl-oxazolidin-2-one **458** in dichloromethane at 0°C followed by addition of crotonaldehyde (Scheme 123). Analysis of the crude ^1H NMR spectrum of this reaction revealed that the desired *syn*-aldolate **463** had been formed in approximately 70% conversion, with approximately 30% of the starting *N*-acyl-oxazolidin-2-one **458** still remaining. This reaction mixture was then purified *via*

chromatography to afford the desired *syn*-aldolate **463** in 60% yield, which was fully characterised.

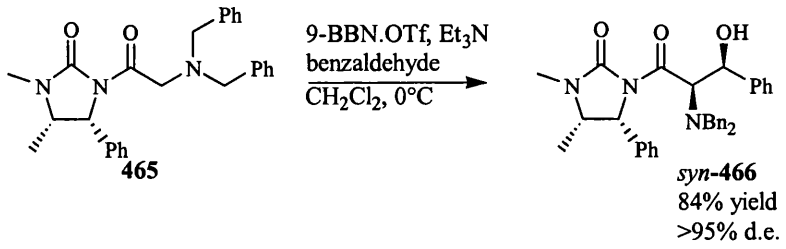


Scheme 123

Repeated attempts to optimise this *syn*-aldol procedure were unsuccessful in my hands however, with no more than 75% conversion of reactants to aldolate product being observed. Thus, whilst using freshly prepared Et_2BOTf as a reagent enabled access to the desired *syn*-aldolate product **463**, the necessity to carry out a tedious chromatographic preparation to remove starting material after each reaction, was clearly unsatisfactory. As a consequence it was decided to explore the use of other boron reagents to facilitate this *syn*-aldol reaction.

3.2.5 9-BBN-Triflate as an effective Lewis Acid for *syn*-selective aldol reactions

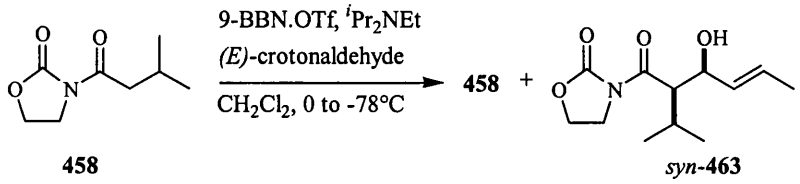
A review of the literature revealed that Caddick *et al.* had reported that treatment of the related *N*-acyl-imidazolidin-2-one **465** with 9-BBN.OTf and base afforded a boron enolate that reacted with benzaldehyde to afford *syn*-aldolate **466** in 84% yield and > 95% d.e. (Scheme 124).[152]



Scheme 124

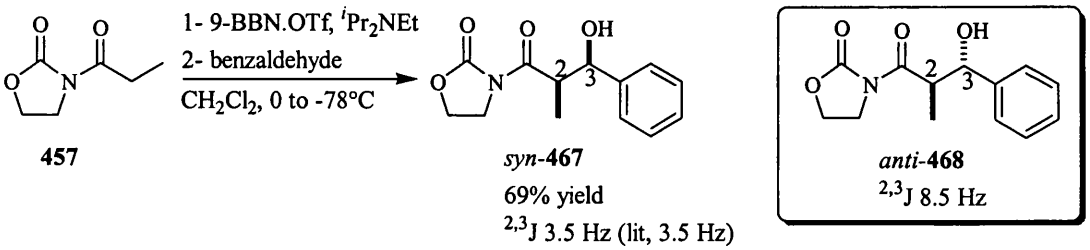
Repeating this chemistry using *N*-acyl-oxazolidin-2-one **458** and crotonaldehyde with a commercially available solution of 9-BBN triflate in hexanes, resulted in the formation of the desired *syn*-aldolate product **463** in 72% yield in very high d.e., and with < 5% of starting material remaining. After carrying out a series of *syn*-aldol reactions using 9-BBN.OTf, optimised reaction conditions were established as follows. The enolate of **458** was prepared in CH_2Cl_2 *via* successive addition of 9-BBN triflate and $^iPr_2NEt$ at 0°C. The

colour of the solution changed from colourless to yellow on addition of 9-BBN triflate, and then back to colourless after the addition of Hünig's base. After a few minutes the reaction vessel was cooled to –78°C, and crotonaldehyde added, the reaction was left at this temperature for one hour, then warmed up to 0°C (Scheme 125).



Scheme 125

Having optimised the preparation of *syn*-aldolate **463** I wanted to confirm the relative stereochemistry of the *syn*-aldolate product that had been prepared using this methodology. Thus, reaction of the boron enolate of *N*-propionyloxazolidin-2-one **457** and benzaldehyde was carried out to afford the known *syn*-aldolate **467** in 69% yield (Scheme 126). This *syn*-aldolate **467** was fully characterised and compared to authentic spectroscopic data available in the literature. Both ^{1}H and ^{13}C NMR spectra reported by Ito *et al.* for *syn*-aldolate **467** matched my spectroscopic data, notably the coupling constant between α-C*H*CH$_3$ and β-C*H*OH was consistent with that reported in the literature of J = 3.5 Hz. This value is in marked contrast to the coupling constant reported for the corresponding *anti*-aldolate **468** of J = 8.5 Hz.[153] It was concluded therefore that these conditions had proven successful in establishing an optimised procedure for the preparation of *syn*-aldolates in a diastereoselective fashion.



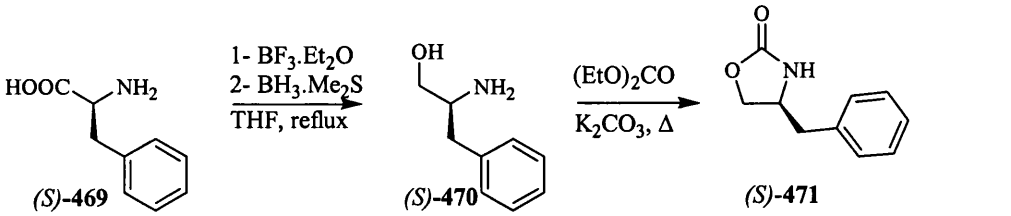
Scheme 126

3.2.6 Asymmetric *syn*-aldol reactions using chiral oxazolidin-2-ones

Since these optimisation studies had established that 9-BBN triflate was the reagent of choice for the preparation of model *syn*-aldolates *(rac)*-**449** in high d.e., my attention next turned to preparing a chiral *syn*-aldolate product using these conditions *via* reaction of the boron enolate of a chiral-*N*-acyl-oxazolidin-2-one **471** with an α,β-unsaturated aldehyde substrate.

3.2.6.1 Preparation of chiral-*N*-acyl-oxazolidin-2-ones

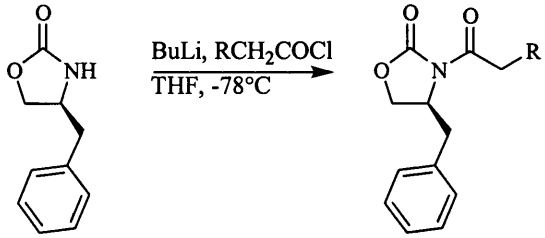
Since enantiopure 4-benzyl-oxazolidin-2-one had previously been shown to afford the best diastereoselectivities for the formation of both *syn*- and *anti*-aldolates,[148,154,149] access to multigram quantities of *(S)*-4-benzyl-oxazolidin-2-one **471** was required. Initial attempts to prepare the precursor amino-alcohol *(S)*-**470** *via* reduction of L-phenylalanine methyl ester with $LiAlH_4$ were only partially successful affording amino-alcohol *(S)*-**470** in only 35% yield. The use of a commercially available solution of $BH_3.Me_2S$ in THF for reduction of the parent α-amino acid **469** was successful however, affording the desired amino-alcohol *(S)*-**470** in 74% yield.[155] Subsequent treatment of *(S)*-**470** with diethylcarbonate as a carbonyl equivalent under basic conditions afforded the 4-benzyl-oxazolidin-2-one *(S)*-**471** in 83% yield whose identity was confirmed *via* spectroscopic comparison with an authentic commercial sample (Scheme 127).



(S)-**471**
62% yield (2 steps)
$[\alpha]_D$+5.5 (c 1.09, ethanol)

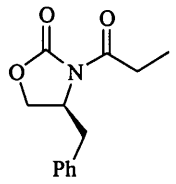
Scheme 127

Two chiral *N*-acyl-oxazolidin-2-ones **423** and **472** (Scheme 128, Figure 33) were then prepared in fair to good yields *via* treatment of the chiral 4-benzyl-oxazolidin-2-one *(S)*-**471** with *n*-BuLi in THF at –78°C, followed by addition of the appropriate acid chloride and warming the reaction mixture to room temperature. Purification of crystalline *(S)*-**423** was afforded *via* recrystallisation from ethyl acetate in 96% yield, whilst *(S)*-**472** was purified *via* silica gel chromatography in 57% yield.

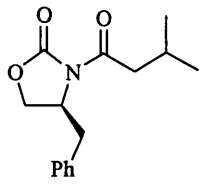


(S)-**471** R = Me, ^{i}Pr

Scheme 128



(S)-**423**
96% yield
$[\alpha]_D$ +100.0 (c 1.02, ethanol)

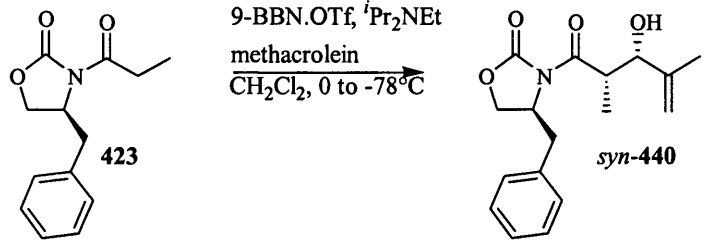


(S)-**472**
57% yield
$[\alpha]_D$ +61.5 (c 1.04, $CHCl_3$)

Figure 33

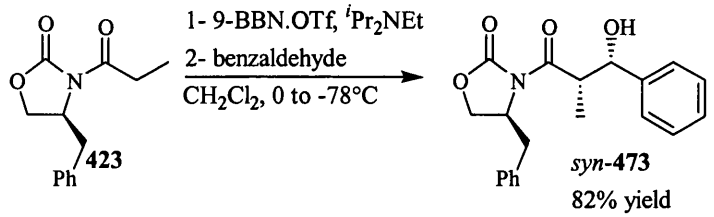
3.2.6.2 Use of chiral *N*-acyl-oxazolidin-2-ones for stereoselective *syn*-aldol reactions

Applying the 9-BBN triflate aldol procedure to *(4S)*-4-benzyl-*N*-propionyloxazolidin-2-one **423** and methacrolein as substrates resulted in the successful formation of *syn*-aldolate **440** in 69% yield and in > 95% d.e. (Scheme 129).



Scheme 129

In order to confirm that the 9-BBN.OTf procedure was indeed affording chiral *syn*-aldolates with the expected stereochemistry, a chiral *syn*-aldolate **473** was prepared that had already been reported and fully characterised in the literature. Thus, the boron enolate of *(S)*-4-benzyl-*N*-propionyloxazolidin-2-one **423** was reacted with benzaldehyde to afford *syn*-aldolate **473** in 82% yield and > 95% d.e. (Scheme 130). The compound was fully characterised and the spectroscopic data was shown to be consistent with those reported previously for *syn*-aldolate **473**.[151]



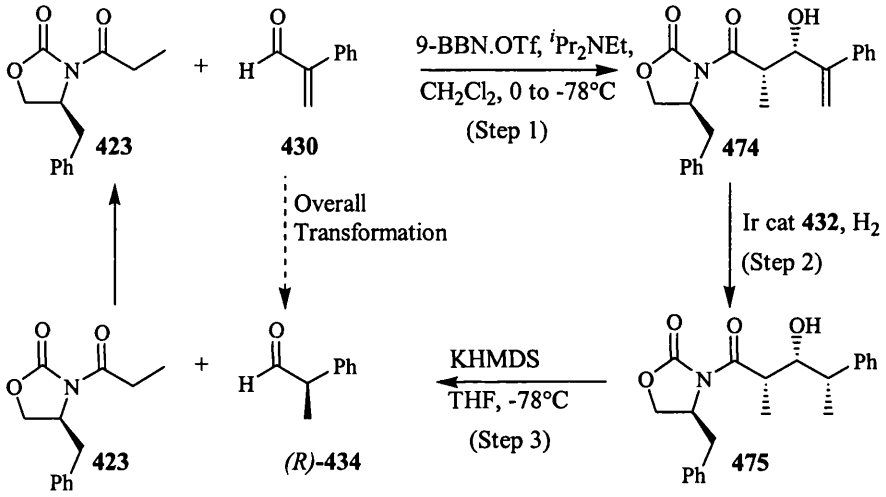
syn-**473**
82% yield
$[\alpha]_D$ +69.8 (c 1.01, CH_2Cl_2)
lit.[149] +75.7 (c 1.00, CH_2Cl_2)

Scheme 130

3.3 Initial attempts to develop an effective *retro*-aldol reaction

3.3.1 Strategy for developing an efficient *retro*-aldol reaction

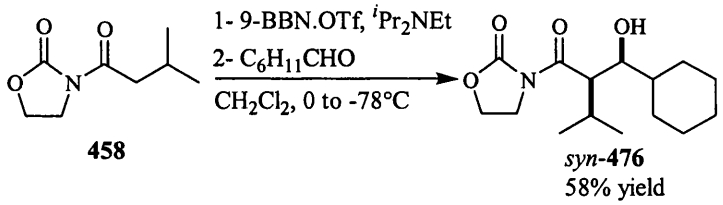
Having demonstrated that I could reproducibly prepare *syn*-aldolates containing an allylic alcohol functionality in good yield and in high d.e. it was clear that Step 1 of the *novel* strategy for using chiral auxiliaries for asymmetric synthesis had been achieved (Scheme 131). Since there was ample literature precedent for carrying out directed reactions on substrates that contained allylic alcohol functionality in high d.e. (Step 2), my attention next turned to the development of effective *retro*-aldol methodology that would enable Step 3 of the protocol described in Scheme 131 to be achieved. Thus, I attempted to identify conditions that would enable *N*-acyl-oxazolidin-2-one-*syn*-aldolates such as **475** to cleanly undergo a *retro*-aldol reaction to afford the parent chiral auxiliary **423** and a chiral aldehyde **434** product.



Scheme 131

3.3.2 Preparation of a suitable *syn*-aldolate substrate for the *retro*-aldol reaction

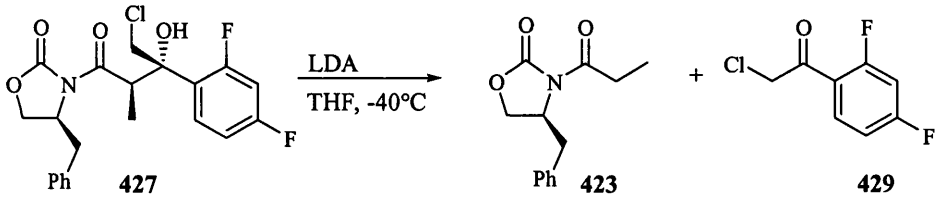
Syn-aldolate **476** was chosen as a substrate for developing an efficient *retro*-aldol reaction because it was similar in structure to the type of *syn*-aldolate product **475** that would be afforded by the directed hydrogenation reaction (Step 2). Consequently, *syn*-aldolate **476** was prepared in 58% yield from *N*-acyl-oxazolidin-2-one **458** and cyclohexane carboxaldehyde using the 9-BBN triflate protocol described in the previous section (Scheme 132).



Scheme 132

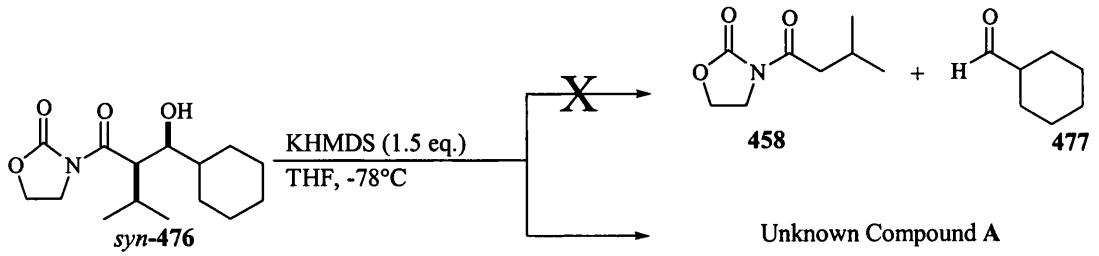
3.3.3 A Failed *retro*-aldol reaction

As described in Section 2.1.3, Bartroli *et al.* had described that deprotonation of ketolate **427** with LDA resulted in a lithium alkoxide that underwent *retro*-aldol reaction to afford *N*-acyl-oxazolidin-2-one **423** and α-chloro ketone **429** in good yield (Scheme 133).



Scheme 133

In light of this precedent, it was reasoned that deprotonation of *syn*-aldolate **476** with a strong base should result in an alkoxide intermediate that would undergo a similar *retro*-aldol reaction. KHMDS was initially chosen as a base for this study because it would result in a potassium alkoxide whose counterion was unlikely to chelate to the oxazolidin-2-one carbonyl, thus ensuring the formation of a highly reactive alkoxide species. Treatment of **476** with KHMDS did not result in the desired *retro*-aldol reaction however, since analysis of the crude ^{1}H NMR spectrum revealed no evidence of resonances corresponding to either the *N*-acyloxazolidin-2-one **458** or aldehyde **477**. Instead, this crude ^{1}H NMR spectrum revealed that this attempted *retro*-aldol reaction had in fact afforded a single new compound **A** in very high yield (Scheme 134).

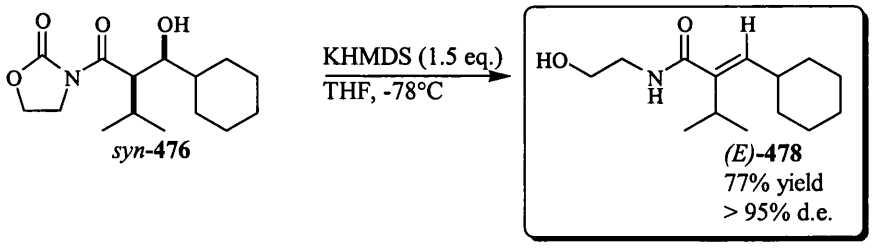


Scheme 134

3.3.4 Structural determination of the unknown product A

Analysis of the ^{1}H NMR spectrum of the unknown product **A** formed in the attempted *retro*-aldol reaction revealed a well-resolved alkene doublet at 5.59 ppm with a coupling constant of J = 7.0 Hz that was coupled to a proton multiplet at 2.25-2.39 ppm. Another feature in the ^{1}H NMR spectrum was a broad peak of low intensity at 6.08 ppm, which was coupled to a methylene resonance appearing as an apparent quartet at 3.44 ppm. Acquisition of the ^{13}C NMR spectrum revealed a single carbonyl resonance at 173 ppm and two olefinic carbon resonances at 138 and 142 ppm. The infra-red spectra of this compound showed three bands of absorption values at 1541, 1619 and 1652 cm^{-1} in the carbonyl region consistent with the formation of an α,β-unsaturated secondary amide fragment. Finally, the molecular ion of **A** was measured at 239 (M^+, EI), indicating a product resulting from loss of CO_2 from the *syn*-aldolate **476**.

With this spectroscopic data in hand, it was proposed that the potassium alkoxide of *syn*-aldolate **476** had undergone an elimination reaction to afford a trisubstituted α,β-unsaturated amide fragment in a diastereoselective fashion. As has been discussed earlier in this thesis, when this type of trisubstituted acid fragment is formed under thermodynamic control the resulting alkene fragment is normally formed with an *(E)*-geometry. Consequently, it was proposed that the potassium alkoxide of *syn*-aldolate **476** had undergone a stereoselective elimination reaction to afford an *(E)*-α,β-unsaturated amide **478** in 77% yield and > 95% d.e. after purification through column chromatography (Scheme 135).



Scheme 135

Fortunately it was found that *(E)*-α,β-unsaturated amide **478** was a crystalline solid which was recrystallised from a 1:2 mixture of ethyl acetate and petrol, to afford crystals that were submitted to X-ray analysis. As can be seen from Figure 34 this structural determination clearly confirmed the proposed structure of amide *(E)*-**478**, with the cyclohexane moiety in its chair conformation *trans* to the amide carbonyl and *cis* to the *iso*-propyl group (Figure 34, Appendix 1).

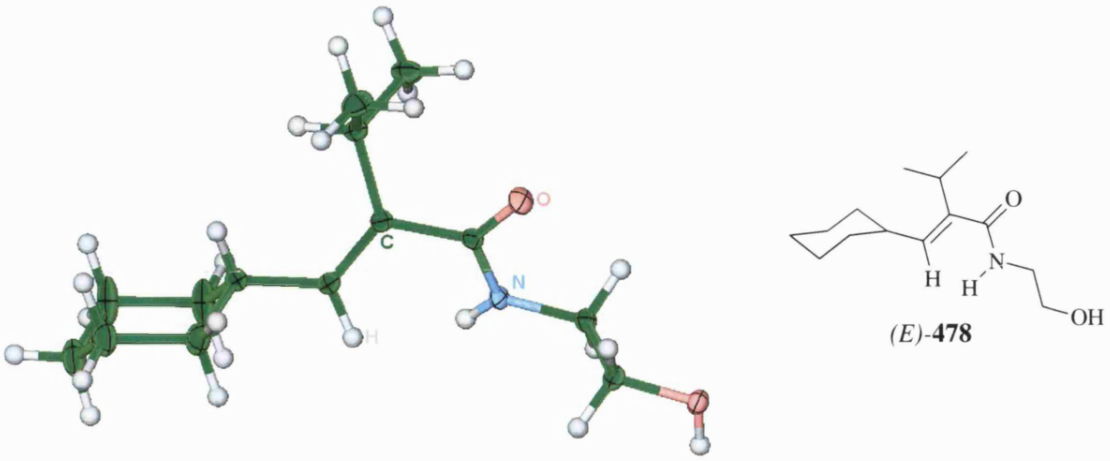


Figure 34. X-ray crystal structure of *(E)*-**478**

This new and fascinating route to α,β-unsaturated amides from *syn*-aldolates appeared to afford a highly stereoselective route to synthetically desirable *(E)*-trisubstituted acid derivatives. As a consequence, it was decided to postpone further investigation into optimising the retro-aldol reaction, in favour of investigating the scope and limitation of this *novel* elimination reaction for a range of achiral *syn*-aldolate substrates.

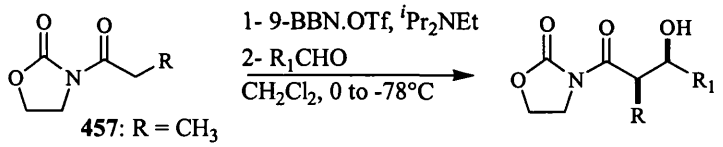
CHAPTER 4. A New Route to trisubstituted *(E)*-α,β-Unsaturated Acid Derivatives

It was decided to investigate further the base-mediated elimination reaction of a range of *syn*-aldolate substrates in order to fully determine the potential of this procedure for the stereoselective synthesis of trisubstituted *(E)*-unsaturated amides.

4.1 Preparation of *(E)*-α,β-unsaturated amides

4.1.1 Preparation of a range of *syn*-aldolate substrates

Firstly, a range of *syn*-aldolate substrates were prepared using 9-BBN-triflate under our optimised conditions in 31-74% yield after purification by chromatography. The low yield obtained for the preparation of **479** (Table 25, entry 1) is due to an observed lack of reactivity in the reaction of the boron enolate of *N*-propionyloxazolidin-2-one **457** with propionaldehyde, since significant amounts of starting material **457** were recovered. In all cases no evidence of any *anti*-aldolate products, was observed in the ^{1}H NMR spectra of the crude reaction product with all aldolates being purified *via* chromatography and fully characterised.



457: R = CH_3
458: R = ^{i}Pr
460: R = CH_2Ph

Scheme 136

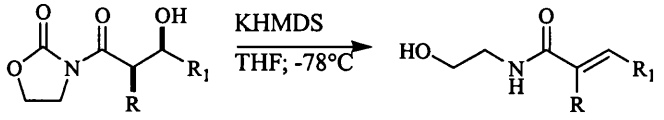
	R	R_1	aldolate		*Common Spectroscopic Features*	
				% yield	δ C*H*R[a]	IR (cm^{-1})[b]
1	CH_3	CH_2CH_3	**479**	31	3.79-3.89 (m)	3471, 1752, 1696
2	^{i}Pr	CH_2CH_3	**480**	48	3.83 (app t)	3463, 1752, 1696
3	CH_3	Ph	**467**	69	4.12 (qd)	3561, 1766, 1682
4	^{i}Pr	Ph	**481**	50	4.48 (dd)	3450, 1751, 1695
5	^{i}Pr	*p*-MeOPh	**482**	60	4.48 (dd)	3449, 1755, 1691
6	CH_2Ph	$(CH_2)_6CH_3$	**483**	74	4.33-4.40 (m)	3474, 1775, 1695

[a] Chemical shifts and multiplicity of C*H*R in the ^{1}H NMR spectra; [b] Frequencies correspond to the carbonyl C=O stretches from oxazolidin-2-one and amide, respectively.

Table 25

4.1.2 Elimination of the potassium alkoxides of *syn*-aldolates to afford *(E)*-amides in high d.e.

Each *syn*-aldolate was then treated with 1.5 equivalents of KHMDS in THF at –78°C for 2 hours, after which time the reaction was quenched with saturated NH_4Cl_{aq}. Examination of the crude ^1H NMR spectra of these reactions indicated that trisubstituted *(E)*-α,β-unsaturated amides **484-489** had been formed in high d.e. and good yield in each case. Each *(E)*-amide was purified to homogeneity *via* chromatography and fully characterised. The *(E)*-stereochemistry of each of these products was confirmed *via* comparison of their spectroscopic data with that of ***(E)*-478** whose structure had previously been established *via* X-ray crystallography, and *via* subsequent hydrolysis to their corresponding acids (*vide supra*) (Scheme 137, Table 26). For amides **484-486** (Table 26, entry 1-3) no evidence for the presence of any *(Z)*-isomer was present in the ^1H NMR spectra of the crude reaction mixtures. For amides **487-489** (Table 26, entry 4-6), diastereomeric excess was assigned *via* integration of the peaks corresponding to the NH peak of both the *(E)*- and *(Z)*-isomers, where the NH resonance of the *(Z)*-isomer always appeared downfield to the NH resonance of the *(E)*-isomer.



syn-**467, 479-483** *(E)*-**484-489**

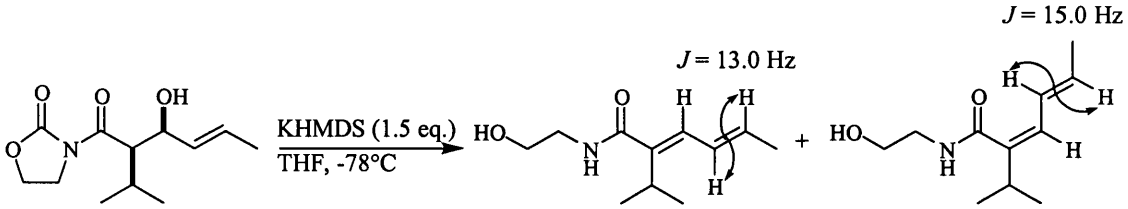
Scheme 137

	R	R_1		*(E)*-amide		*Common Spectroscopic Features*	
				% d.e.	% yield[a]	δ C*H*R	IR (cm^{-1})
1	CH_3	CH_2CH_3	**484**	> 95	67	6.19 (br s), 6.38 (t)	1538, 1615, 1701
2	^{i}Pr	CH_2CH_3	**485**	> 95	99	5.77 (t), 6.26 (br s)	1534, 1617, 1653
3	CH_3	Ph	**486**	> 95	91	6.48 (s), 7.19 (br s)	1575, 1620, 1644
4	CH_3	Ph	**486**	80[b]	Not isol.	-	-
5	^{i}Pr	Ph	**487**	92	94 (69)	6.33 (br s), 6.79 (s)	1538, 1612, 1641
6	^{i}Pr	*p*-MeOPh	**488**	90	95 (64)	6.38 (br s), 6.73 (s)	1542, 1620, 1645
7	Bn	$(CH_2)_6CH_3$	**489**	92	95 (73)	6.17 (br t), 6.54 (t)	1537, 1620, 1656

[a] Yields in bracket correspond to yields afforded after chromatographic purification for characterisation purposes; [b] Reaction was carried out at 0°C. The crude reaction product was not purified.

Table 26

During investigations into the scope and limitation of this novel methodology a significant limitation of this elimination procedure was discovered for *syn*-aldolate substrates that derived from α,β-unsaturated aldehydes. Thus, treatment of *syn*-aldolate **463** previously prepared for optimisation studies of the aldol reaction (see section 3.2.5) with KHMDS afforded a crude reaction product with a complex ^{1}H NMR spectrum arising from the presence of two compounds that were assigned as the *(E,E)*-α,β,γ,δ-unsaturated amide **490**, and its geometric isomer *(Z,E)*-**491** in 60% d.e. (Scheme 138). The d.e. of this elimination reaction was determined *via* integration of the resonances of the *iso*-propyl methyl protons in the ^{1}H NMR spectrum of the crude reaction mixture. Attempted chromatographic purification of this mixture of geometric isomers through silica gel did not result in any separation, however these *(E,E)*- and *(Z,E)*-isomers could be separated *via* chromatography over a stationary phase derived from silica gel that had been coated with silver nitrate. Indeed this purification technique allowed isolation of both the major *(E,E)*-isomer and the minor *(Z,E)*-isomer which were independently characterised *via* ^{1}H NMR spectroscopy. These *(E,E)*-**490** and *(Z,E)*-**491** isomers were found to isomerise on standing however, so they could not be fully characterised in a conventional manner, however the mass spectra of the resultant mixture of isomers **490** and **491** did reveal a molecular ion peak of 197 (M^+, EI) (Scheme 138). Since these samples darkened significantly over time it was suspected that they contained residual traces of silver nitrate that had catalysed the observed *(E)*/*(Z)* isomerisation in the presence of light.



syn-**463**

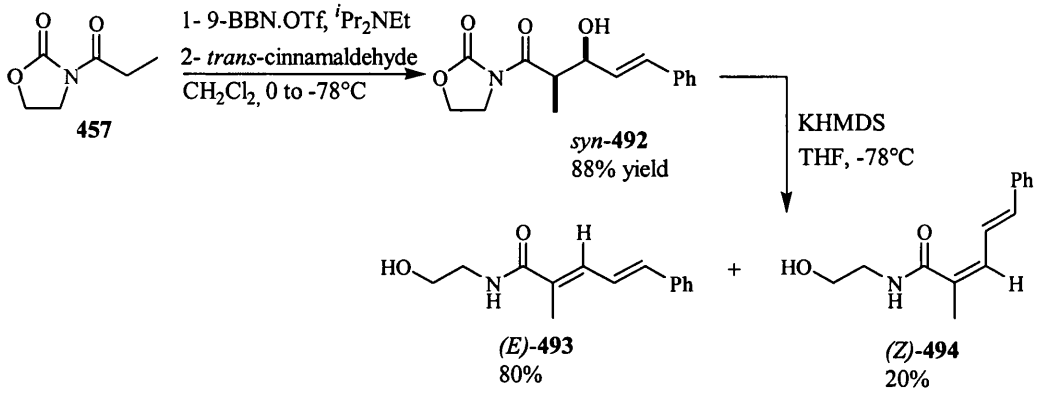
(E,E)-**490**
80%
δ_{NH} 6.33 ppm

(Z,E)-**491**
20%
δ_{NH} 6.13 ppm

Scheme 138

In order to determine if this lack of stereoselectivity during the elimination of *syn*-aldolates derived from α,β-unsaturated aldehydes was a general trend, *syn*-aldolate **492** was next prepared *via* reaction of the boron enolate of *N*-propionyloxazolidin-2-one **457** with *trans*-cinnamaldehyde in 88% yield and in > 95% d.e. This *syn*-aldolate **492** was then treated with 1.5 equivalents of KHMDS in THF at -78°C in the usual manner to afford a mixture of *(E)*- and *(Z)*-unsaturated amides **493** and **494** once again in only 60% d.e. (Scheme 139). Fractional recrystallisation of this mixture of geometric isomers from ethyl acetate was

successful in affording the major diastereoisomer in 64% yield, which was assigned as trisubstituted *(E,E)*-α,β-unsaturated amide **493** by analysis of its spectroscopic data and subsequent cleavage to its parent acid (*vide supra*). It should be noted that the first time this reaction was carried out ^{1}H NMR spectroscopic analysis of the crude product appeared to indicate that *(E,E)*-**493** had been formed in > 95% d.e. However, this d.e. could not be repeated and as a consequence it appears that this value was incorrect and must have arisen from unintentional fractional recrystallisation of the crude reaction product.



Scheme 139

In conclusion, the base mediated elimination of γ,δ-unsaturated-*syn*-aldolates **463** or **492** was not as stereoselective as the other *syn*-aldolates **430, 467, 479-483** employed as substrates in this study.

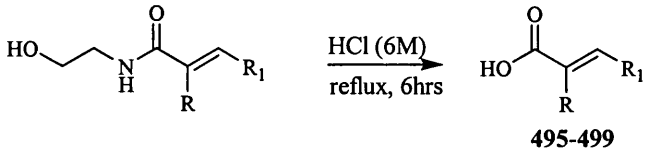
4-2 Preparation of *(E)*-α,β-unsaturated carboxylic acids and (*E*)-α,β-unsaturated oxazolines

Having demonstrated that this elimination methodology afforded an excellent general route to *(E)*-trisubstituted α,β-unsaturated amides, their conversion to other carboxylic acid derivatives was next explored in order to expand the synthetic versatility of this methodology.

4.2.1 Hydrolysis of trisubstituted *(E)*-α,β-unsaturated amides to afford their corresponding *(E)*-acids

Conditions were next investigated that would enable aqueous hydrolysis of *(E)*-amides to afford their corresponding carboxylic acids *(E)*-**495-499** in good yield. Thus, five representative *(E)*-α,β-unsaturated amide **478, 484, 486, 489** and **493** were refluxed in 6M HCl_{aq} for 6 hours. Problems were initially encountered in extracting the water soluble *(E)*-acid products **495-499** from aqueous solution, however a work-up protocol involving saturating the aqueous solution with sodium chloride prior to extraction into ethyl acetate

gave the corresponding *(E)*-acids **495-499** in excellent yield. Importantly, care had to be taken during removal of organic solvent from some of these *(E)*-acids because of their volatility, leading to significant loss in mass on exposure to reduced pressure over time (Scheme 140, Figure 35).



495-499

Scheme 140

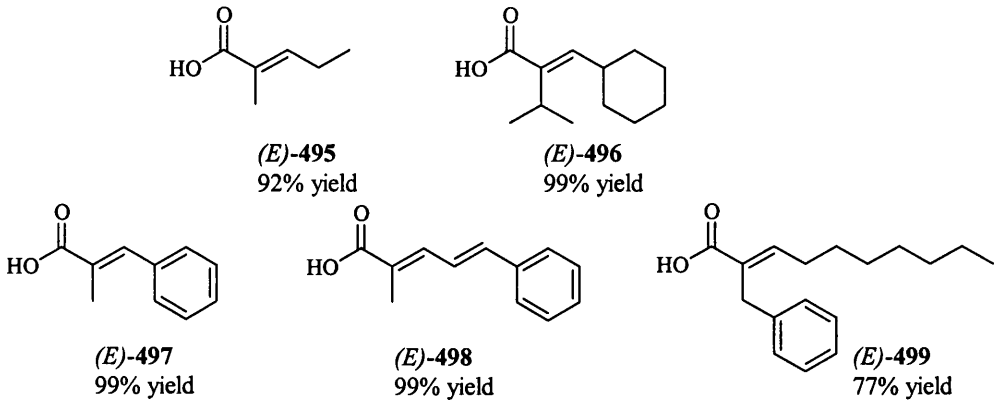


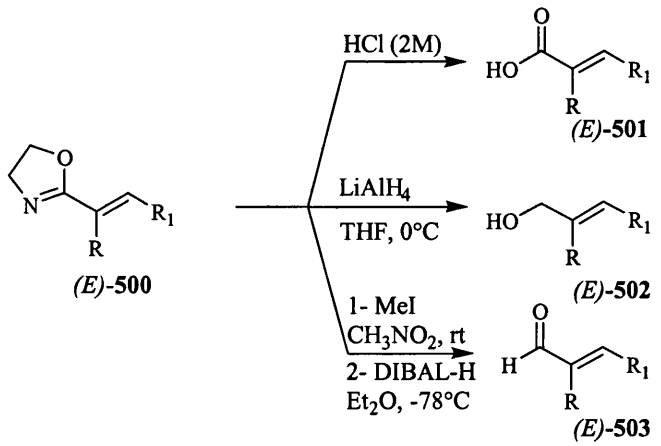
Figure 35

Importantly, examination of the crude ^{1}H NMR spectra of these hydrolysis reactions revealed that all of these α,β-unsaturated acids had been formed as *single* isomers with no evidence of any alkene migration having occurred under the strong acid conditions used for hydrolysis. Finally, the structures and stereochemistry of *(E)*-acids **495** and **497** were confirmed *via* comparison with commercially available samples of *(E)*-2-methylpentenoic acid and *(E)*-2-methyl-3-phenylpropenoic acid, whilst spectroscopic data of *(E)*-**496** and *(E)*-**498** were compared with known literature values.[156,157] It should be noted that these structural assignments for *(E)*-acids **495-499** provide further evidence for the original assignment of *(E)*-stereochemistry to amides **484-489** discussed in section 4.1.2.

4.2.2 Conversion of trisubstituted *(E)*-α,β-unsaturated amides into their corresponding *(E)*-oxazolines.

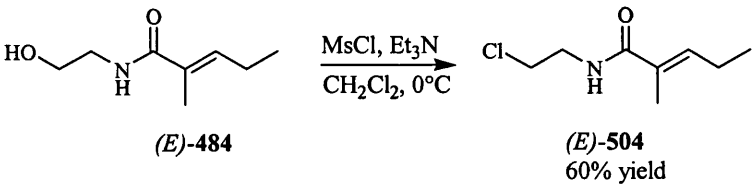
The synthetic versatility of this methodology was further demonstrated *via* cyclisation of the *N*-hydroxyamide fragment of the *(E)*-amides to afford their corresponding trisubstituted *(E)*-α,β-unsaturated oxazolines. It was reasoned that access to synthetically versatile *(E)*-oxazolines **500** would allow future combinatorial access to a range of *(E)*-acids **501**,

(E)-alcohols **502**, or even *(E)*-aldehydes **503** using the range of hydrolytic reductive protocols described in Scheme 141.[158,159]



Scheme 141

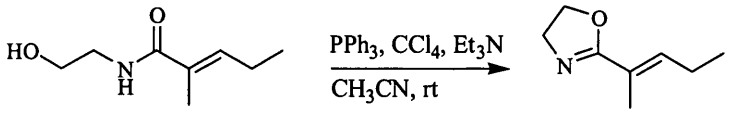
A number of different approaches were attempted to achieve this aim before an effective protocol was identified for the conversion of tiglate derived *(E)*-amide to its corresponding *(E)*-oxazoline. For example, treatment of *(E)*-α,β-unsaturated amide **484** with mesylchloride and triethylamine in CH_2Cl_2 at 0°C, followed by washing with sodium hydroxide, gave a single product in 60% yield which was tentatively assigned as chloride **504** (Scheme 142).[160]



Scheme 142

An alternative protocol by Vorbruggen *et al.*,[161] involving treatment of amide *(E)*-**484** with triphenylphosphine, carbon tetrachloride and triethylamine in acetonitrile was partially successful, affording *(E)*-oxazoline **505** in only 40% yield after purification by column chromatography (Scheme 143). The structure of oxazoline **505** was confirmed *via* analysis of the ^1H NMR spectrum which no longer showed the broad peaks characteristics of OH and NH resonances of amide *(E)*-**484**, whilst the four methylene protons from the *N*-hydroxyamide in amide **484** had shifted to a higher frequency. The infrared spectra of this compound showed two bands of absorption values at 1653 and 1700 cm^{-1} consistent with the presence of an unsaturated oxazoline fragment. Finally, the mass spectrum of **505** was

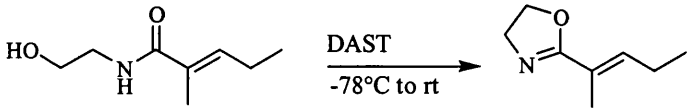
measured at 139 (M^+, EI), indicating a product consistent with loss of H_2O from amide **484**.



(E)-**484** *(E)*-**505**
40% yield

Scheme 143

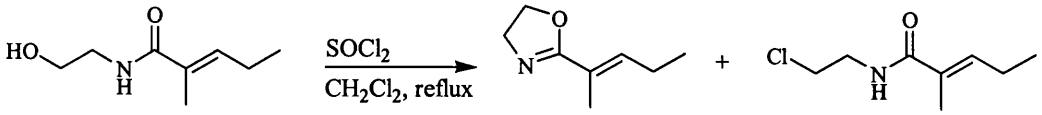
Alternatively, a procedure by Curran *et al.* was carried out involving treatment of *(E)*-**484** with the expensive reagent diethyl ammonium sulfur trifluoride DAST (1.3 eq.) at –78°C for 6 hours, followed by stirring at room temperature overnight, which once again resulted in formation of trisubstituted *(E)*-oxazoline **505**, but in only 45% isolated yield (Scheme 144).[162]



(E)-**484** *(E)*-**505**
45% yield

Scheme 144

In an attempt to address these low yields I next refluxed α,β-unsaturated amide **484** with 2.5 equivalents of $SOCl_2$ for 2 hours to afford a crude reaction mixture which contained a 3:2 mixture of the oxazoline *(E)*-**505** and chloride *(E)*-**504** (Scheme 145).[163] Reasoning that the reaction was proceeding *via* a mechanism in which *(E)*-amide **484** was first converted to chloride **504**, followed by cyclisation of chloride **504** to afford the desired *(E)*-oxazoline **505**, the length of the reaction was increased to 48 hours. Surprisingly, this did not lead to an increase in the amount of *(E)*-oxazoline product **505** formed, but instead gave a 20:1 mixture of chloride **504** to *(E)*-oxazoline **505**.



(E)-**484**		*(E)*-**505**	*(E)*-**504**
	12 hours	3	2
	48 hours	1	20

Scheme 145

This result clearly indicated that the initially low yield observed in this reaction was not a consequence of the parent *(E)*-amide **484** failing to cyclise to afford the *(E)*-oxazoline **505**, but instead was due to attack of adventitious chloride ion on the *(E)*-oxazoline (as its HCl

salt **506**) to afford its corresponding *(E)*-chloride **504** *via* the mechanism described in Figure 36.

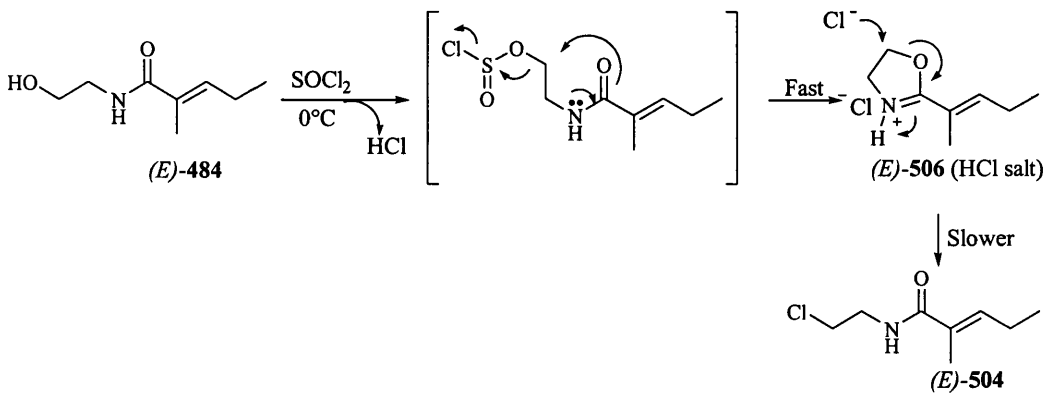
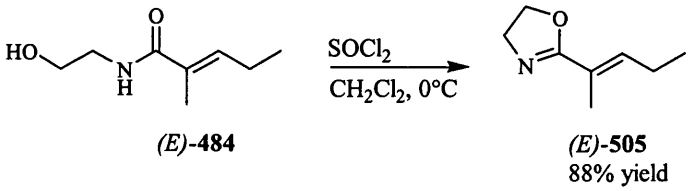


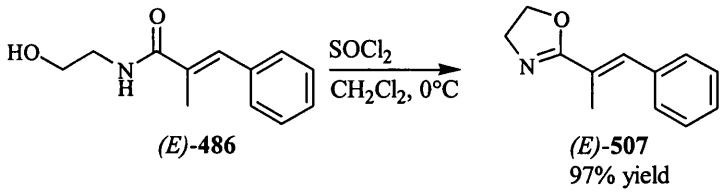
Figure 36

With this information in hand, thionyl chloride (5 eq.) was added in a dropwise fashion to an ice-cold solution of unsaturated amide **484** in CH_2Cl_2 followed by stirring at 0°C for 2 hours before work-up *via* slow addition of sodium hydroxide (5M), to afford the desired *(E)*-oxazoline **505** in 88% yield (Scheme 146).



Scheme 146

These conditions were then applied to a second trisubstituted *(E)*-α,β-unsaturated amide **486** to afford *(E)*-trisubstituted α,β-unsaturated oxazoline **507** in 97% yield, thus demonstrating the general applicability of this protocol for the cyclisation of *(E)*-amide substrates arising from my *novel* elimination methodology (Scheme 147).



Scheme 147

Whilst time considerations restricted the range of *(E)*-oxazolines that have been prepared using this methodology, as well as preventing me from demonstrating the potential of these type of oxazolines *(E)*-**500** to afford acids *(E)*-**503**, alcohols *(E)*-**504** or aldehydes *(E)*-**505** (see Scheme 141), there is ample literature precedent to suggest that these type of trisubstituted *(E)*-oxazolines will prove to be versatile synthons. Indeed, a more complete

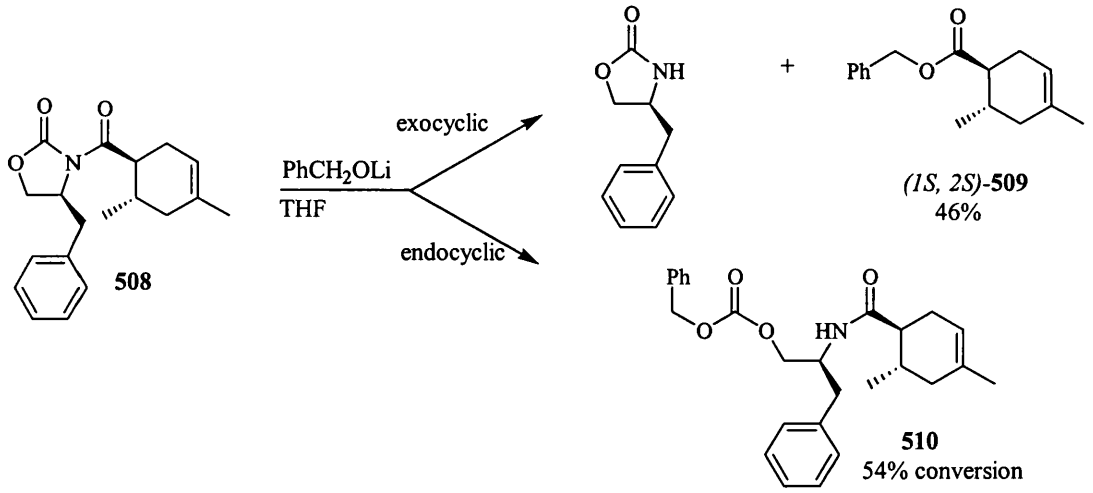
study on the potential of these type of α-substituted unsaturated oxazolines for the development of novel asymmetric protocols is currently being carried out by a member of the SDB research group.

CHAPTER 5. Probing the Mechanism of the Elimination Reaction of *N*-acyl-oxazolidin-2-one Aldolates

Since treatment of a range of *syn*-aldolates with KHMDS had been shown to afford *(E)*-α,β-unsaturated amides in a highly stereoselective manner, the mechanism of this elimination reaction was next explored.

5.1 Mechanistic Hypothesis

It is well known that sterically unhindered *N*-acyl oxazolidin-2-ones can undergo endocyclic ring cleavage *via* either inter- or intramolecular attack of oxygen nucleophiles at their oxazolidin-2-one carbonyl groups.[164,165] For example, reaction of Diels-Alder adduct **508** and lithium benzyloxide had been shown to afford the endocyclic cleavage product **510** as the major product, as well as the desired benzylester **509** in 46% conversion (Scheme 148).



Scheme 148

Consequently, it was proposed that the stereochemical outcome of the elimination reaction of the potassium alkoxides of *syn*-aldolates **511** could be explained by invoking an intramolecular endocyclic cleavage mechanism. Thus, a potassium alkoxide **512** would initially undergo intramolecular attack at the oxazolidin-2-one carbonyl resulting in O-O carbonyl migration, to afford a 1,3-oxazinane-2,4-dione alkoxide intermediate **513**. Subsequent anion equilibration of alkoxide **513** to afford enolate **514** would then enable

stereoselective elimination of carbon dioxide to occur to afford the trisubstituted secondary amide *(E)*-**515** in high d.e. (Figure 37).

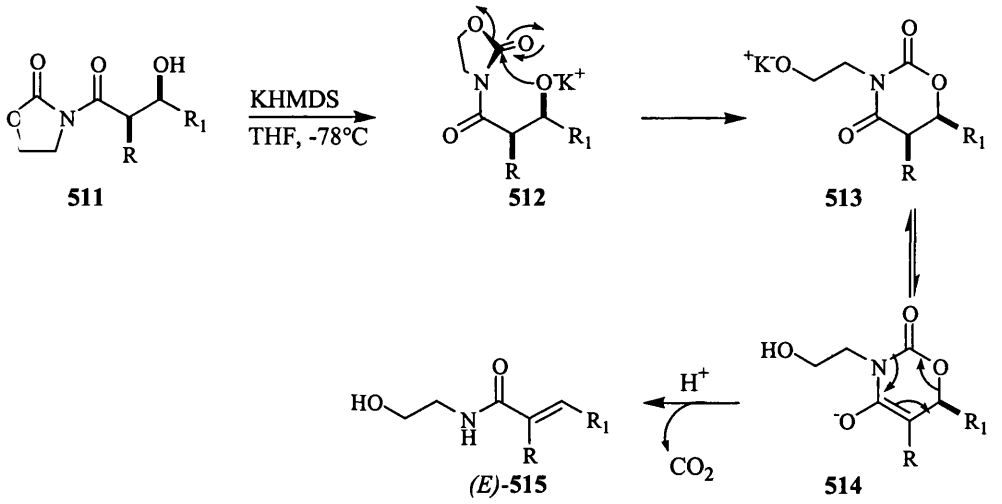


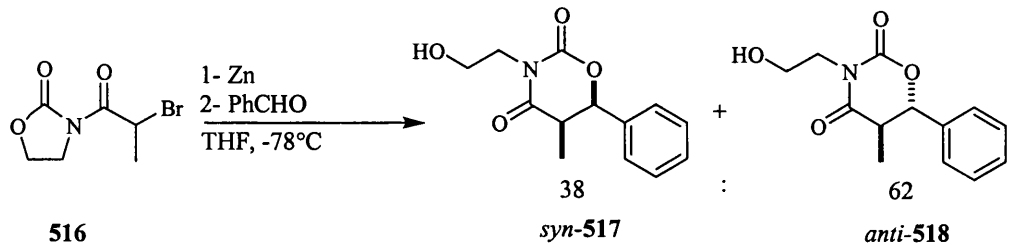
Figure 37. Intramolecular cyclisation/elimination mechanism for the formation of *(E)*-α,β-unsaturated amides **515.**

Whilst this mechanism appeared perfectly feasible it was important to obtain clear proof that the formation of an oxazinanedione intermediate was responsible for stereocontrol in this reaction, and I therefore attempted to find conditions that would enable selective conversion of *syn*-aldolate **511** into its corresponding oxazinane-2,4-dione, which would then be employed for elimination studies.

5.2 Isolation of a possible intermediate

5.2.1 Literature precedent for rearrangement of *syn*-aldolates to oxazinane-2,4-diones

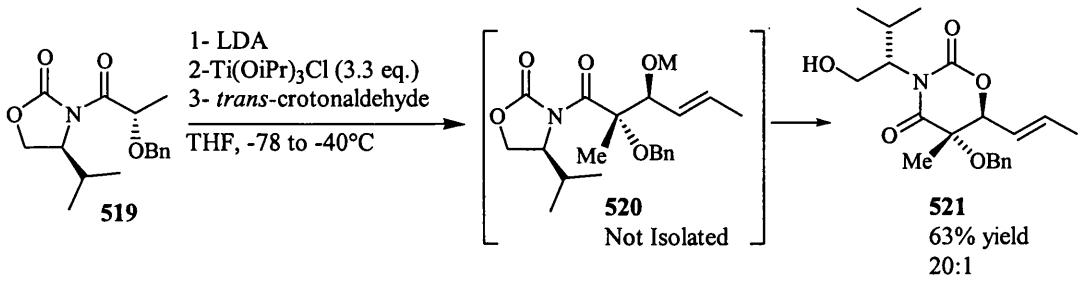
A review of the literature revealed two previous examples where alkoxides of β-hydroxy-*N*-acyloxazolidin-2-ones had selectively rearranged to afford products containing an oxazinane-2,4-dione skeleton. Ito *et al.* had reported that reaction of a zinc enolate prepared from α-bromo-*N*-acyl-oxazolidin-2-one **516** with benzaldehyde at 0°C had not afforded the expected adolate products but instead had given a mixture of rearranged 1,3-oxazinane-2,4-dione diastereoisomers **517** and **518** in good yield but in poor d.e. (Scheme 149).[153]



516 *syn*-517 *anti*-518

Scheme 149

In a second report, Kobayashi *et al.* described in 2001 that treatment of the titanium enolate of *N*-acyloxazolidinone **519** with *trans*-crotonaldehyde once again did not afford the expected aldolate product **520**, but instead gave the rearranged oxazinanedione **521** in good d.e. (Scheme 150).[166]



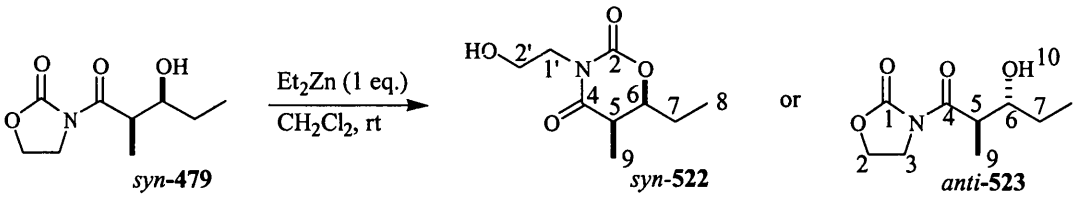
519 **520** Not Isolated **521** 63% yield 20:1

Scheme 150

5.2.2 An effective protocol for the rearrangement of *syn*-aldolates to afford oxazinane-2,4-diones

Since these observations implied that titanium or zinc alkoxides of β-hydroxy-*N*-acyloxazolidin-2-ones could undergo facile rearrangement to their corresponding 1,3-oxazinane-2,4-diones, it was decided to investigate whether generating zinc alkoxides of *N*-acyl-oxazolidin-2-one-*syn*-aldolates **511** would result in selective rearrangement to afford 1,3-oxazinane-2,4-dione products. Thus, treatment of a solution of *syn* aldolate **479** with a stoichiometric amount of Et_2Zn in CH_2Cl_2 cleanly afforded a single product **A** which was tentatively assigned as the desired oxazinane-2,4-dione **522** using the following spectroscopic arguments (Scheme 151). Analysis of the ^1H NMR spectrum revealed that unlike *syn*-aldolate **479**, the C*H*CH_3 and C*H*Et protons of product **A** were well-resolved and appeared respectively at δ 2.79 ppm as a quartet of doublets and δ 4.34 ppm as a doublet of doublets of doublets. Likewise the ^{13}C NMR spectrum revealed that the corresponding carbon resonances appeared at δ 39.6 and δ 40.8 ppm in *syn*-aldolate **479** whilst in product **A** they were respectively shifted downfield at δ 38.0 ppm and upfield at δ 48.1 ppm. Both carbonyl absorptions at 1750 and 1695 cm^{-1} were similar to those of the starting aldolate **479** (1752, 1696 cm^{-1}), with no difference in the chemical shift of the

carbonyl resonances in ^{13}C NMR, whilst the molecular ion of **A** was measured at 202 (MH^+, CI^+), confirming the molecular formula of the product as $C_9H_{16}NO_4$. Whilst the spectroscopic data described for product **A** was consistent with the formation of the desired oxazinane-2,4-dione skeleton, this data was also consistent with the structure of an alternative *anti*-aldolate **523** product that could potentially have been formed from the zinc alkoxide of *syn*-aldolate **479** undergoing a reversible *retro*-aldol/aldol reaction.

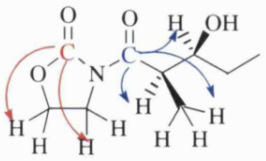


syn-**479** *syn*-**522** *anti*-**523**

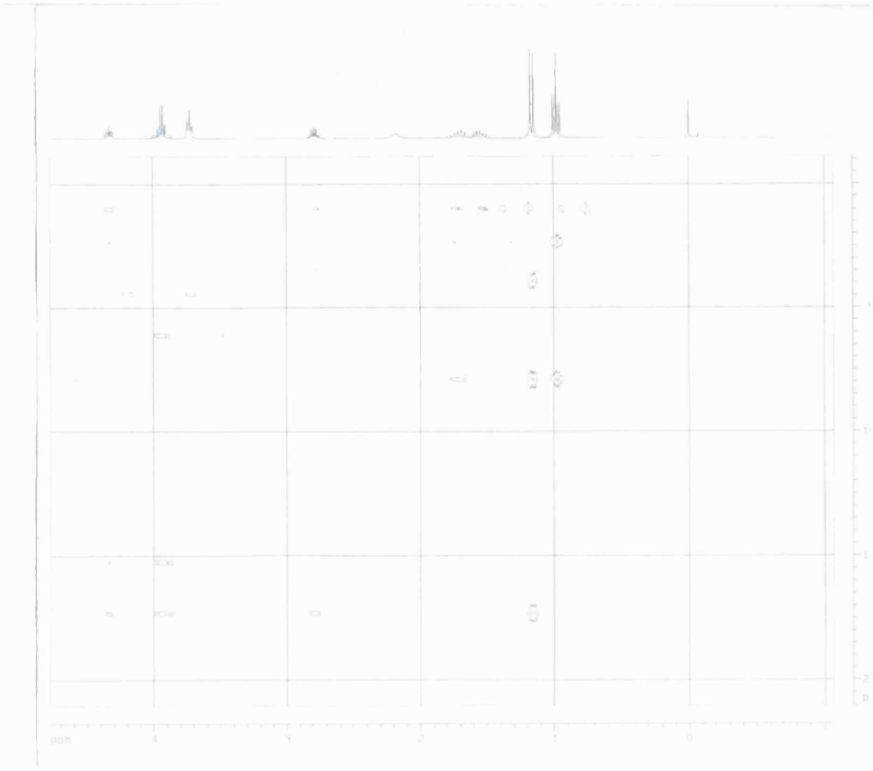
Scheme 151

This potential assignment problem was solved by carrying out a long range carbon-hydrogen NMR correlation experiment that demonstrated coupling between carbon and proton resonances that were connected to each other by up to three bonds. Thus, carrying out this long range coupling correlation experiment on product **A** (Figure 38) revealed coupling between the ^{13}C resonance of the C2 carbonyl and ^{1}H resonances corresponding to H5, H6, 2xH7, 2xH1'and 2-CH2'OH protons (for oxazinane-2,4-dione **522**); whilst the C4 carbonyl ^{13}C resonance was coupled with H5, H6, 2xH7, 2xH1'and 2xCH2'OH and the C5-CH_3 protons (for oxazinane-2,4-dione **522**). This connectivity pattern was clearly incompatible with the structure of *anti*-aldolate **523**, which whilst demonstrating the same type of coupling pattern between its C4 carbonyl and its 2xH2, 2xH3, H5, H6, H7 and H9 protons, would only have afforded three cross-peaks between its C1 carbonyl and its 2xH2, 2xH3 and H5 resonances. This NMR correlation spectra clearly revealed therefore, that the structure of rearranged product **A** was consistent with the oxazinane-2,4-dione skeleton *syn*-**522**, and *not* with the structure of *anti*-aldolate product **523**.

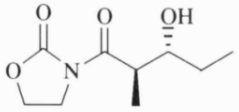
Since this approach appeared to provide a facile route from *N*-acyl-oxazolidin-2-one-*syn*-aldolates to afford oxazinane-2,4-diones, it was decided to explore further this rearrangement reaction. Optimisation studies on *syn*-aldolate **479** revealed that the rearrangement reaction could be initiated using a catalytic amount of Et_2Zn affording the same oxazinane-2,4-dione product **522** in an essentially identical 58% yield (Scheme 152).



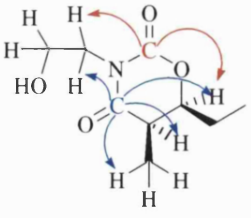
syn-**479**



Possible structures for A:

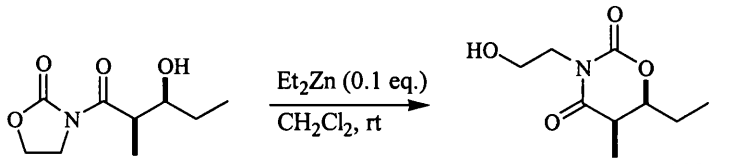


aldolate product
anti-**523**



oxazinane-1,4-dione
syn-**522**

Figure 38

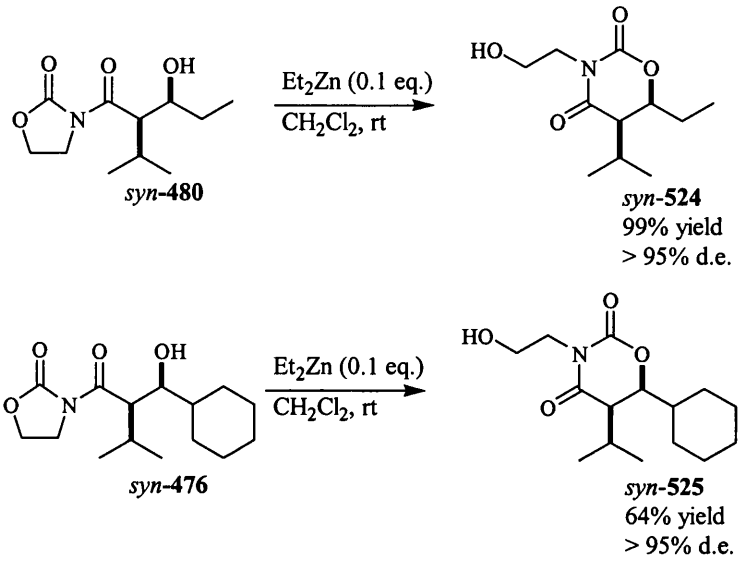


syn-**479**

syn-**522**
58% yield
> 95% d.e.

Scheme 152

These catalytic conditions were subsequently employed for the rearrangement of two more *syn*-aldolates **480** and **476**, where treatment with a catalytic amount of Et_2Zn in CH_2Cl_2 resulted in formation of *syn*-oxazinanediones **524** and **525** in good yield (Scheme 153).



syn-**480**

syn-**524**
99% yield
> 95% d.e.

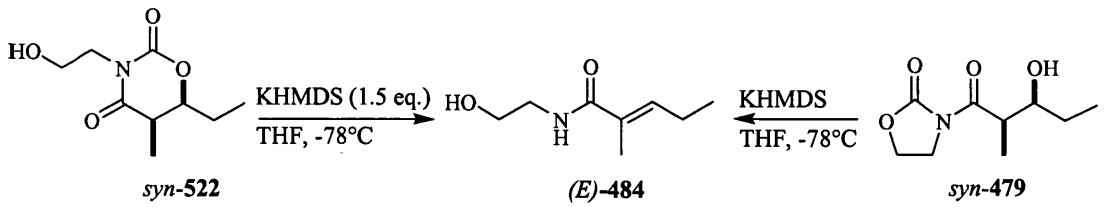
syn-**476**

syn-**525**
64% yield
> 95% d.e.

Scheme 153

5.2.3 Elimination of *syn*-oxazinane-2,4-diones affords trisubstituted (*E*)-α,β-unsaturated amides in high d.e.

With an authentic sample of *syn*-oxazinane-2,4-dione **522** in hand it was explored whether treatment with KHMDS would result in a stereoselective elimination reaction to form *(E)*-amide **484** in high d.e. Thus, treatment of *syn*-oxazinane-2,4-dione **522** with KHMDS in THF at -78°C resulted in clean elimination to afford trisubstituted *(E)*-α,β-unsaturated amide **484** in > 95% d.e. (Scheme 154). It should be noted that the d.e. obtained for the formation of amide *(E)*-**484** in this reaction was *identical* to that obtained previously for elimination of *syn*-aldolate **479**, thus providing compelling evidence that oxazinane-2,4-dione alkoxide is a common intermediate responsible for the excellent levels of stereocontrol observed in both types of stereoselective elimination reactions.

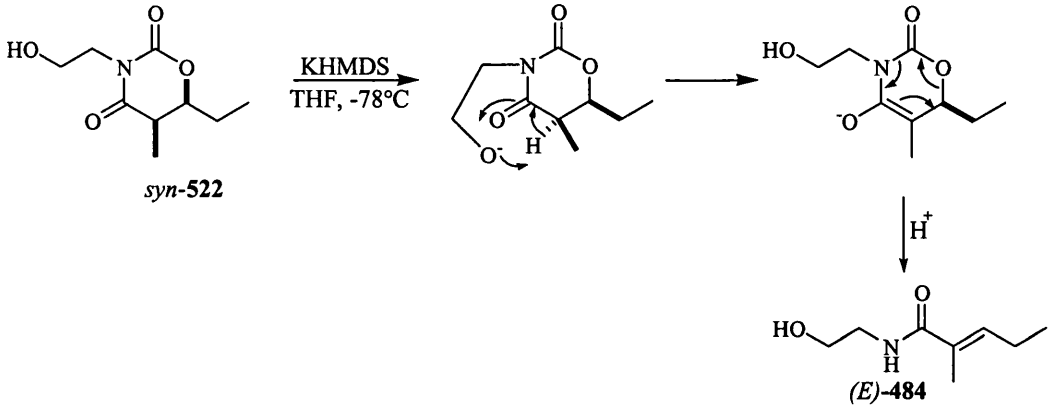


syn-**522** (*E*)-**484** *syn*-**479**

Scheme 154

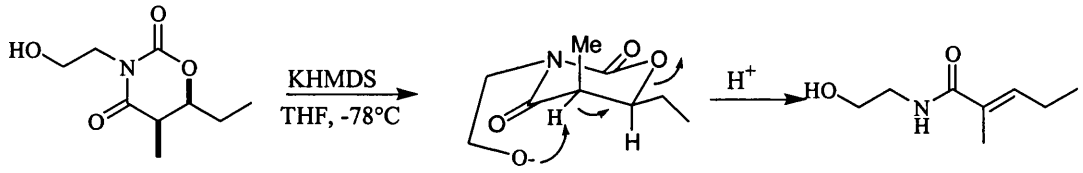
5.3 Probing the mechanism of the elimination reaction

Having established that oxazinane-2,4-diones were plausible intermediate in the base mediated stereoselective elimination reaction of *syn*-aldolates to afford *(E)*-amides, it was necessary to establish whether the key elimination reaction of CO_2 from this oxazinane-2,4-dione intermediate **522** was likely to occur *via* a stepwise E1cB-type pathway, or *via* a concerted E2 elimination pathway (Figure 39).



syn-**522** (*E*)-**484**

Proposed E1cB mechanism for elimination of *syn*-oxazinane-2,4-dione intermediate **522**



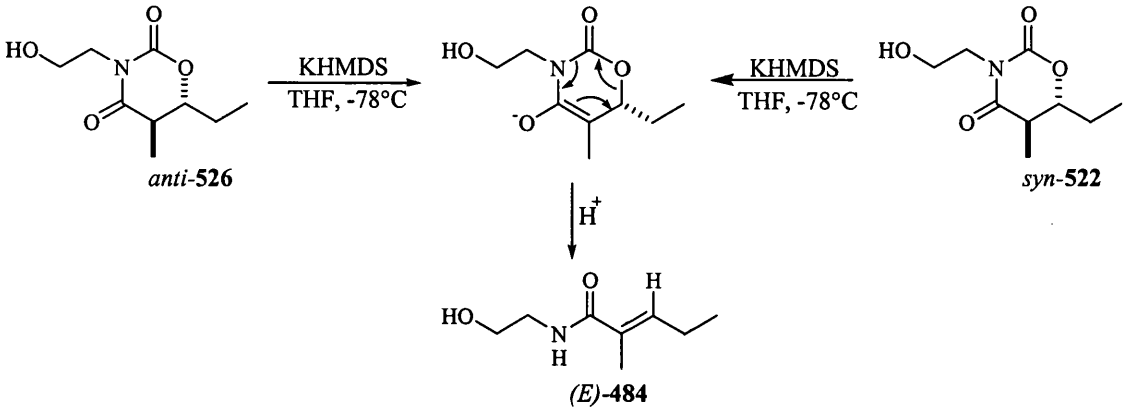
syn-**522** (*E*)-**484**

Alternative E2 mechanism for elimination of *syn*-oxazinane-2,4-dione intermediate **522**

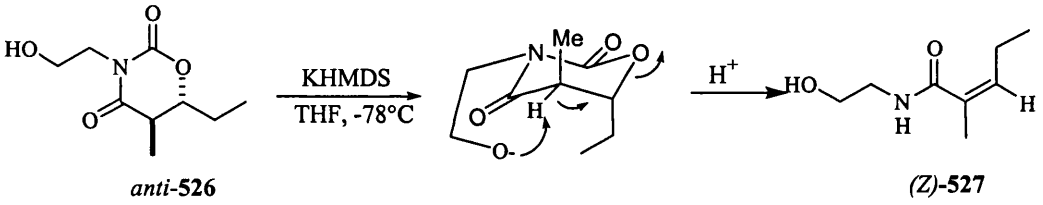
Figure 39

In order to probe which of these two elimination mechanisms was occurring, it was decided to compare the stereoselectivity of elimination of potassium alkoxides of a *syn*-aldolate with its corresponding *anti*-aldolate substrates, since changing the relative stereochemistry of the aldolates would have important stereochemical consequences depending on whether an E1cB or E2 elimination pathway was in operation. Thus, for an

E1cB reaction pathway, it was predicted that elimination of both *syn*- and *anti*-aldolate substrates would proceed *via* a common enolate-like intermediate that would eliminate CO_2 to afford the *same (E)*-α,β-unsaturated amide **484** (Figure 40). Alternatively, for a concerted E2 elimination reaction, it would be expected that the stereochemistry of both aldolate substrates would be conserved throughout, with antiperiplanar elimination of *syn*-oxazinane-2,4-dione intermediate **522** affording an *(E)*-α,β-unsaturated amide **484**, whilst *anti*-**526** would afford the corresponding *(Z)*-α,β-unsaturated amide **527**.



E1cB elimination of an *anti*-oxazinane-2,4-dione **526** will result in a *(E)*-amide **484**



E2 elimination of an *anti*-oxazinane-2,4-dione **526** will result in a *(Z)*-amide **527**

Figure 40

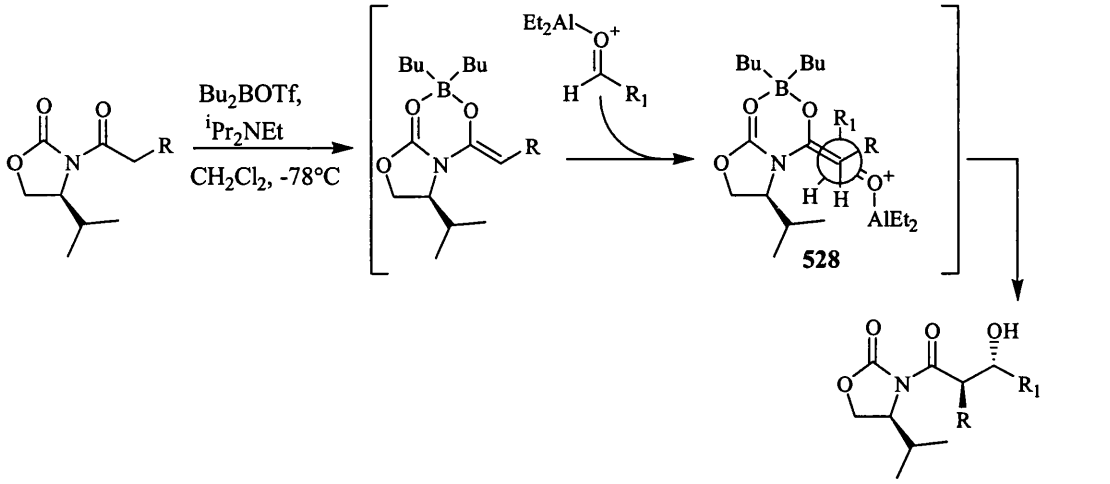
It was therefore necessary to develop an efficient protocol for the preparation of an *anti*-aldolate substrate that would enable these comparative elimination reactions to be carried out.

5.3.1 The *anti*-stereoselective aldol reaction using *N*-acyl oxazolidin-2-ones

5.3.1.1 Background

Heathcock *et al.* have reported previously on a protocol that enables selective access to *anti*-aldol diastereoisomers.[149] Thus, treatment of the boron *(Z)*-enolate of an *(S)*-*N*-acyl-oxazolidin-2-one with an aldehyde precoordinated to Et_2AlCl had resulted in the formation of the *(2S,3S)*-*anti*-aldolate **529** in high d.e. It was proposed that Et_2AlCl acts as a bulky Lewis acid due to a relatively short *O-Al* bond, which results in a transition state **528** that

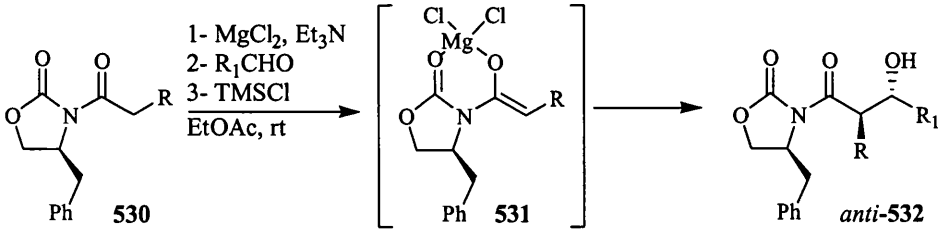
minimises steric interaction between the Et_2AlCl and both the R-alkyl group of the enolate and the R_1-alkyl group of the aldehyde, thus affording *anti*-aldolate **529** in high d.e. (Scheme 155).



anti-'Non-Evans'-isomer **529**

Scheme 155

During the course of my investigation, Evans *et al.* described an alternative method to obtain the alternative *anti*-aldolate of *N*-acyl-oxazolidin-2-ones. He reported that treatment of *(R)*-4-benzyl-*N*-acyl-oxazolidin-2-one **530** with a catalytic amount of magnesium chloride and an excess of triethylamine and chlorotrimethylsilane gave *anti*-aldolate **532** with good conversion rates and selectivity under very mild conditions at room temperature.[167,154] The catalytic reaction was limited by a narrow substrate specificity profile however, with only aromatic and conjugated aldehydes affording good yields of *anti*-aldolate products, whilst bulky R-substituents at the α-position of the *N*-acyl-oxazolidin-2-one **530** were not well tolerated (Scheme 156).



Scheme 156

The mechanism of this reaction has not been yet elucidated, although Evans has ruled out the possibility of a Mukaiyama aldol pathway in which an enolsilane is formed and attacks the electrophilic aldehyde complexed to a Lewis acid species.[168] Indeed, the independently prepared enolsilane of **530** was shown not to react with benzaldehyde in the presence of $MgCl_2$ in ethyl acetate. Instead, Evans proposed that a nucleophilic magnesium enolate **531**

reversibly attacked the aldehyde to form a magnesium aldolate product **533**. Silylation of aldolate **533** displaces the magnesium counterion from the alkoxide fragment, irreversibly affording the silyl-aldolate **534**. The magnesium catalyst is then displaced by another molecule of *N*-acyl-oxazolidin-2-one **530**, thereby completing the catalytic cycle (Figure 41).[154]

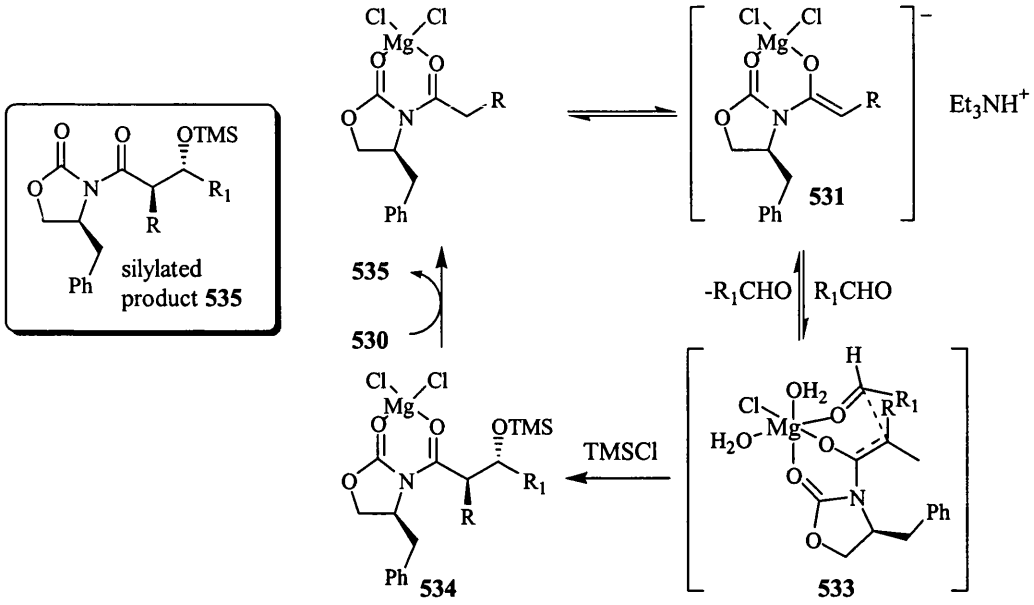


Figure 41

Evans proposed that the aldol reaction of magnesium enolate gave *anti*-aldolate **535** *via* a six-membered transition state. Computational calculations predicted that formation of the alternative *anti*-aldolate **536** was disfavoured due to steric interaction between the benzyl stereodirecting group and the incipient aldehyde. Thus, the alternative *anti*-aldolate **536** was formed in high d.e. under these conditions (Figure 42).

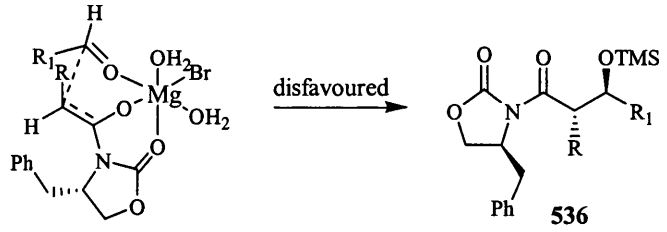
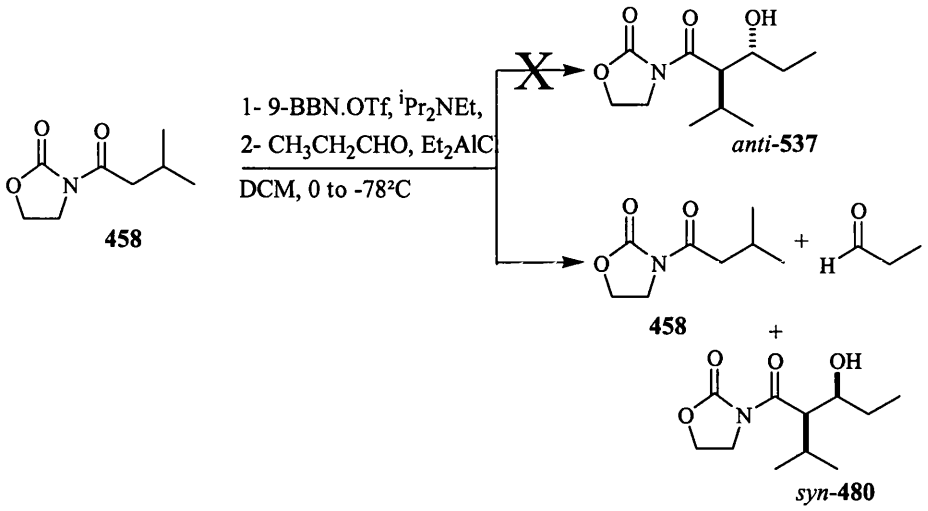


Figure 42

5.3.1.2 Preparation of *anti*-aldolate substrates for stereospecific elimination studies

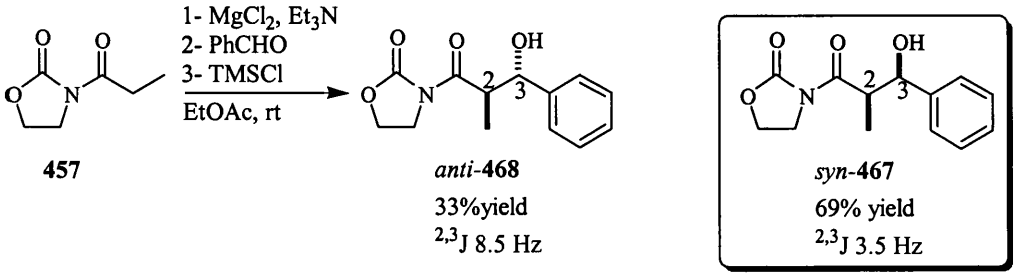
My attempts to repeat Heathcock's *anti*-aldolate chemistry were universally unsuccessful. Repeated attempts involving addition of the boron enolate of *N*-acyloxazolidin-2-one **458** in CH_2Cl_2, to a solution of propionaldehyde pre-complexed with Et_2AlCl never afforded

any of the desired *anti*-aldolate product **537**, instead giving either recovered starting material **458**, or the corresponding Evans' *syn*-aldolate product **480** (Scheme 157).



Scheme 157

The alternative Evans' procedure involving addition of the magnesium enolate of *N*-acyloxazolidin-2-one **457** to benzaldehyde was successful however, affording the desired *anti*-aldolate **468** as a single stereoisomer, *albeit* in a low 33% yield (Scheme 158). The stereochemistry of the *anti*-aldolate **468** was confirmed *via* examination of its ^{1}H NMR spectra which revealed a large coupling constant between α-C*H*CH_3 and β-C*H*OH of J = 8.5 Hz. This compares with the smaller coupling constant of J = 3.5Hz for the corresponding *syn*-aldolate **467** which was also prepared in 69% yield using the 9-BBN triflate *syn*-aldol protocol described previously (see section 3.2.5).

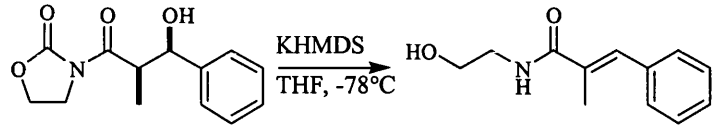


Scheme 158

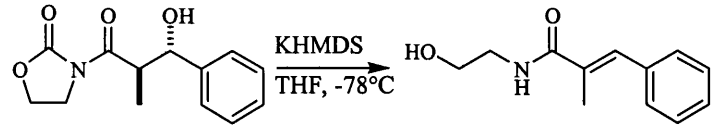
5.3.2 Elimination of the potassium alkoxide of *N*-acyl-oxazolidin-2-one aldolates is non-stereospecific

With both *syn*-aldolate **467** and *anti*-aldolate **468** in hand, the key elimination reactions involving separate treatment of each of the *syn*-**467** and *anti*-**468** diastereoisomers with 1.5 equivalents of KHMDS in THF at -78°C were carried out. As expected, the potassium alkoxide of *syn*-aldolate **467** cleanly eliminated to afford *(E)*-*N*-(2-hydroxyethyl)-2-

methyl-3-phenyl-2-propenamide **486** in a good 90% yield and in > 95% d.e. Under the same conditions the potassium alkoxide of *anti*-aldolate **468** also underwent stereoselective elimination reaction, affording the *same* *(E)*-*N*-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide **486** in similar yield and in *identical* d.e. (Scheme 159), thus providing good evidence that these reactions occur *via* E1cB-type reactions that proceed through a common oxazinane-2,4-dione-intermediate.



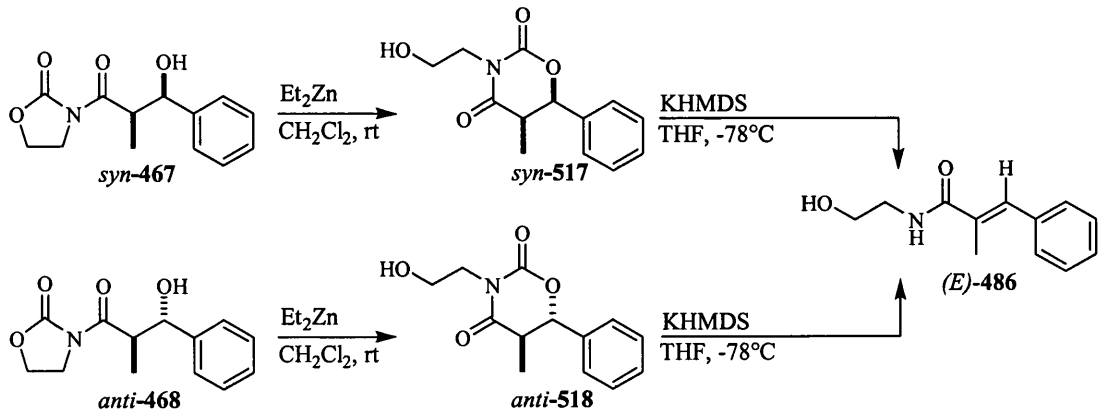
syn-**467** *(E)*-**486** > 95% d.e.



anti-**468** *(E)*-**486** > 95% d.e.

Scheme 159

In order to provide further proof that a common oxazinane-2,4-dione enolate intermediate was responsible for stereocontrol in both these elimination reaction, *syn*-aldolate **467** and *anti*-aldolate **468** were treated with a catalytic amount of diethylzinc in CH_2Cl_2 at room temperature, to afford *syn*-oxazinane-2,4-dione **517** in 90% d.e. and *anti*-oxazinane-2,4-dione **518** in > 95% d.e. respectively. The ^1H NMR spectra of oxazinanediones *syn*-**517** and *anti*-**518** revealed coupling constants between C*H*CH_3 and C*H*Ph of 3.5 and 11.5 Hz respectively. Both *syn*- and *anti*-oxazinanedione **517** and **518** were then separately treated with 1.5 equivalents of KHMDS in THF at –78°C, with both substrates once again affording *(E)*-α,β-unsaturated amide **486** in good yield and in the same > 95% d.e. (Scheme 160).



syn-**467** *syn*-**517** *(E)*-**486** *anti*-**468** *anti*-**518**

Scheme 160

5.3.3 Mechanistic rationale

The series of experiments described in this chapter are clearly consistent with the potassium alkoxides of *syn*-aldolates and *anti*-aldolates undergoing stereoselective elimination to afford the same *(E)*-α,β-unsaturated amide *via* a common oxazinane-2,4-dione intermediate according to the original reaction mechanism described in Figure 39 and 40. Thus, deprotonation of either *syn*-aldolate **467** or *anti*-aldolate **468** will afford alkoxides that rearrange stereoselectively to afford the potassium alkoxides of *syn*-oxazinane-2,4-dione **538** and *anti*-oxazinane-2,4-dione **540** respectively, each of which is in equilibrium with a common oxazinane-2,4-dione enolate intermediate **539** (Figure 42). Thus, in this mechanism, the stereochemistry that originates from the C1 stereocentre of each aldolate substrate is always destroyed, with the stereochemistry of the *(E)*-α,β-unsaturated amide being controlled during irreversible elimination of CO_2 from enolate **539** *via* an E1cB type pathway.

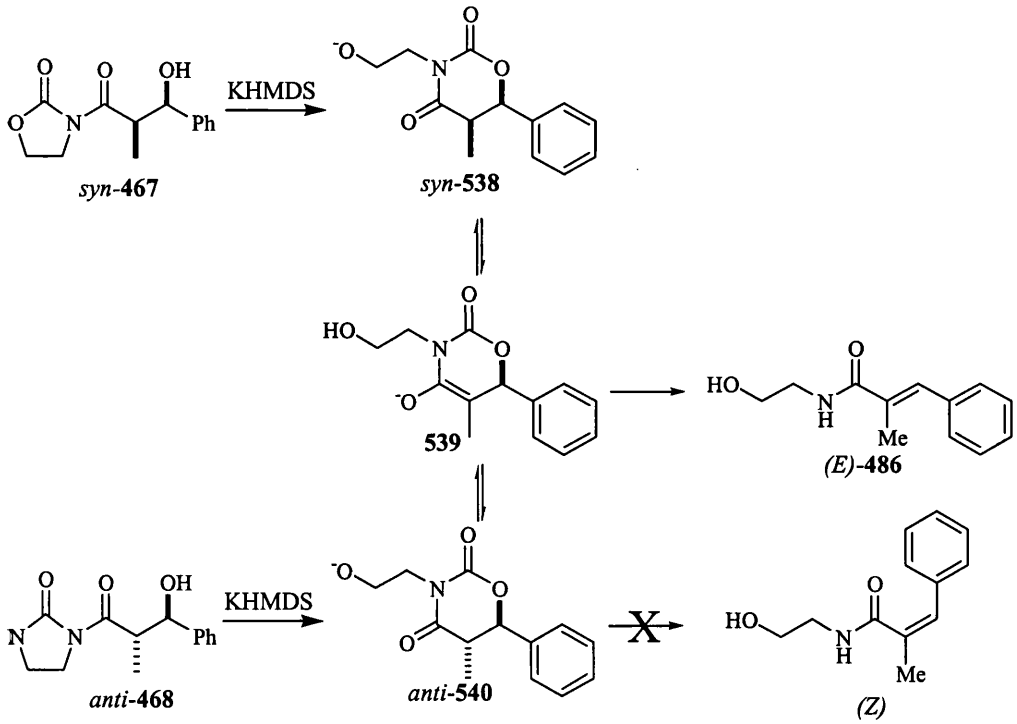
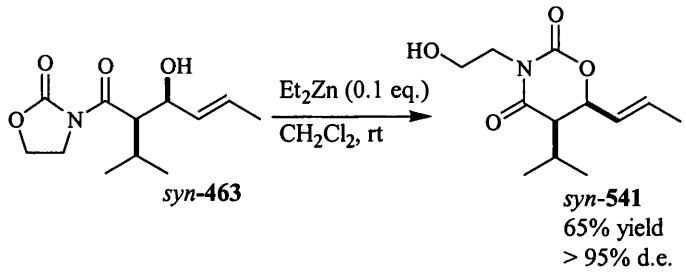


Figure 42

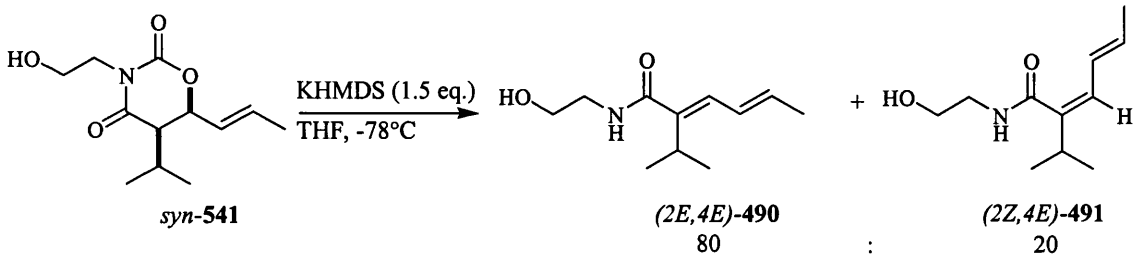
Previously in this thesis it has been described that the potassium alkoxide of *syn*-aldolate **463** eliminated to afford a mixture of unsaturated *(E)*- and *(Z)*-amides in only 60% d.e. I wished to probe whether this loss of stereocontrol occurred during rearrangement of *syn*-aldolate **463** to its oxazinane-2,4-dione intermediate **541**, or during the resulting elimination of this oxazinane-2,4-dione **541** to afford the amide products. Treatment of

syn-aldolate **463** with KHMDS resulted in a zinc alkoxide, which cleanly rearranged to afford oxazinane-2,4-dione **541** as a single isomer (Scheme 161).



Scheme 161

The oxazinanedione **541** (> 95% d.e.) was then treated with KHMDS under the same conditions used previously to eliminate *syn*-aldolate **463** to α,β-unsaturated amide, and was shown to afford the same ratio of *(E)*- and *(Z)*-α,β-unsaturated amide **490** and **491** in 60% d.e. (Scheme 162).



Scheme 162

Thus, for this particular type of *syn*-aldolate substrate **463**, rearrangement to the corresponding *syn*-oxazinanedione **541** appears to be completely stereoselective, with any loss in stereocontrol occurring during the resulting elimination reaction of CO_2 to form a mixture of *(E)*- and *(Z)*-α,β-unsaturated amides **490** and **491** (Figure 43).

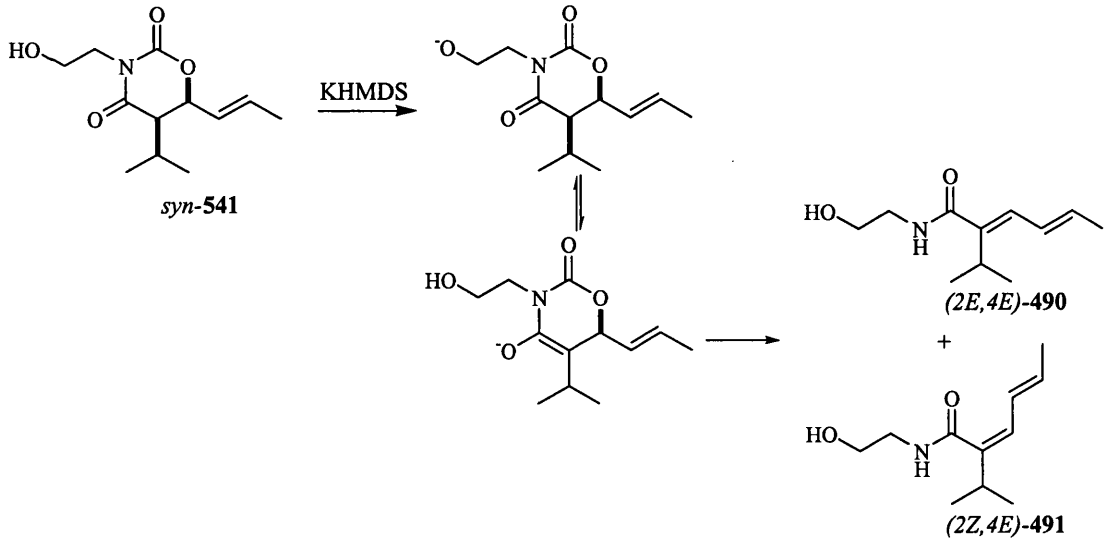


Figure 43

5.3.4 Molecular modelling studies on the elimination of oxazinane-2,4-dione enolates

The mechanistic investigations in this chapter have clearly revealed that the *(E)*- or *(Z)*-stereochemistry of the trisubstituted amide products produced *via* base mediated elimination of *syn*- or *anti*-aldolates was determined during the E1cB elimination step of oxazinane-2,4-dione enolate **514** (Figure 45).

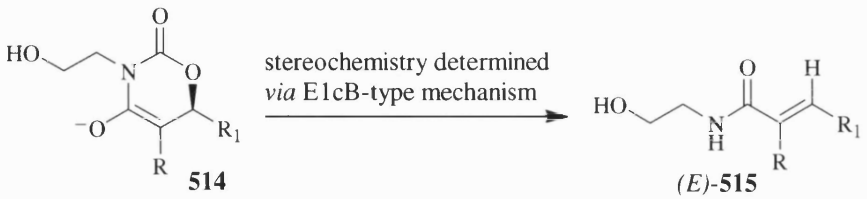


Figure 45

As has been described previously in this thesis, *(E)*-trisubstituted esters are normally formed in preference to *(Z)*-trisubstituted esters when elimination reactions occur under thermodynamic control. However in this case it appears likely that the elimination reaction was occurring under kinetic control via concerted elimination of oxazinane-2,4-dione **514**. In order to further understand the reasons why this E1cB reaction was preferentially affording *(E)*-amides in high d.e., I have collaborated with Dr David Fox of the University of Cambridge who has carried out preliminary molecular modelling studies on the transition states of simplified models leading to the formation of amides *(Z)*-**542** and *(E)*-**543** (Figure 46).

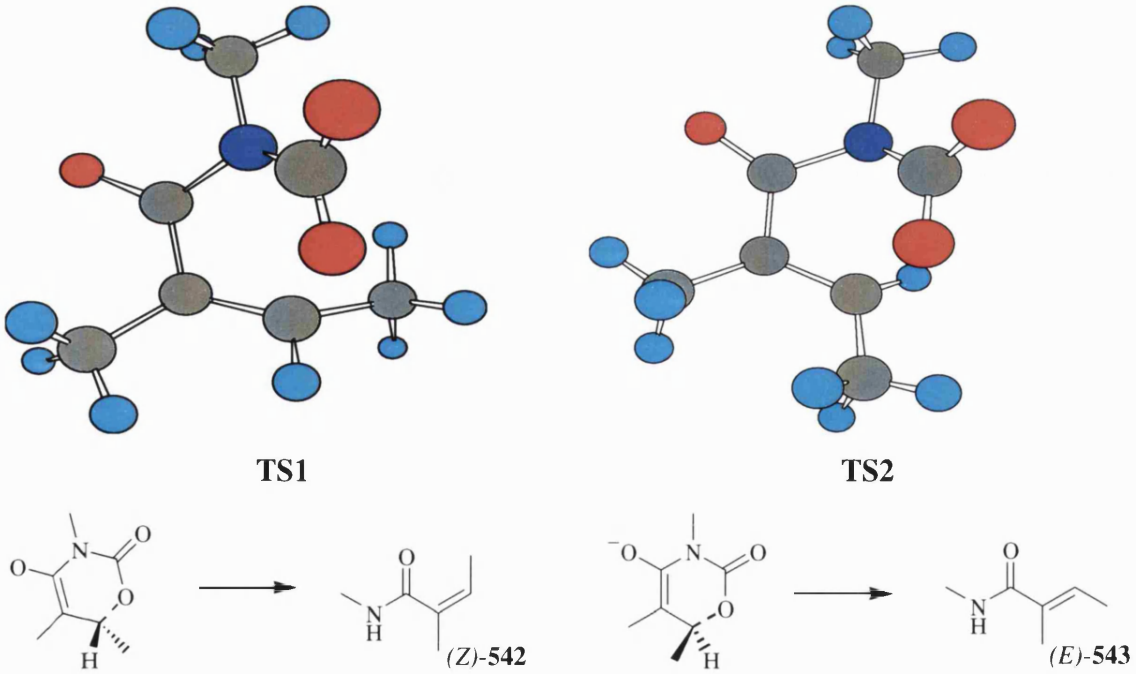


Figure 45

Calculations were performed using the Windows PC version of GAMESS using the MP2 method and a 6-31(d,p)++ basis set, which revealed that transition state **TS 1** leading to the *(Z)*-amide **542** was 16 kJ mol-1 greater in energy than transition state **TS 2** leading to the *(E)*-amide **543** . This transition state energy difference is very large, and at –78°C represents a large difference in relative reaction rates, thus providing good evidence in support of the selective formation of *(E)*-amides under kinetically controlled conditions.

CHAPTER 6. Broadening the Range of Aldolate Substrates employed for Elimination

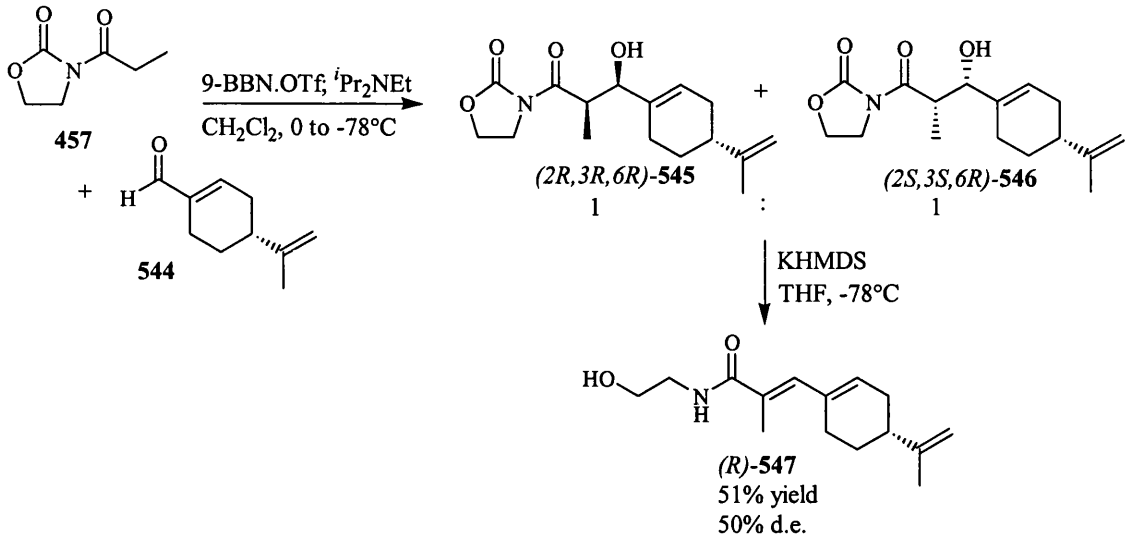
The *novel* elimination reaction of *N*-acyl-oxazolidin-2-one aldolates that has been described appeared to be attractive methodology that could potentially rival the Wittig or Horner-Wadsworth-Emmons procedures for the preparation of *(E)*-trisubstituted acid derivatives. It was therefore decided to explore the versatility of this methodology to demonstrate that aldolates derived from chiral aldehydes, or heteroaryl aldehydes, would also undergo stereoselective elimination reactions.

6.1 Elimination of *syn*-aldolates derived from chiral aldehydes

Since most natural products of interest are derived from *(E)*-trisubstituted α,β-unsaturated acid fragments (or derivatives) containing a methyl group at their α-position, I concentrated on the preparation of three chiral trisubstituted *(E)*-amides containing this functionality.

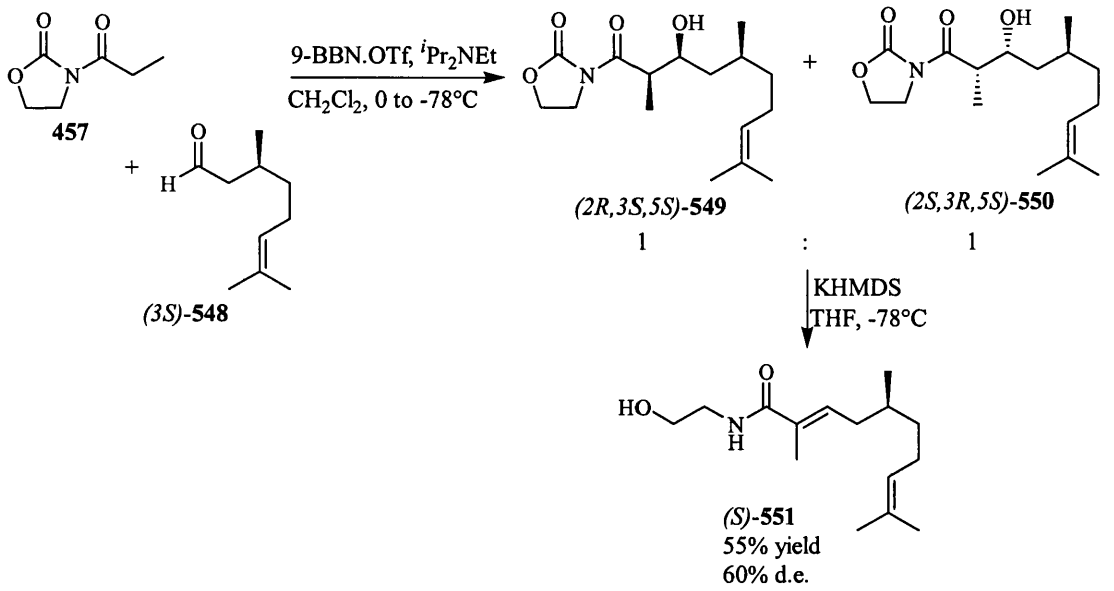
Reaction of the boron enolate of achiral *N*-propionyl-oxazolidin-2-one **457** with *(R)*-perillaldehyde **544** (90% pure) resulted in a mixture of two diastereoisomers in 64% yield. Attempted purification of this mixture of diastereoisomers *via* exhaustive chromatography was unsuccessful and did not afford any enhancement in diastereoisomeric purity, and as a consequence this reaction was characterised as a mixture of diastereoisomers. The ^{1}H NMR spectrum of the mixture was too complex to reveal the d.e., however the relative heights of the resonances for the two diastereoisomers in the ^{13}C NMR spectrum showed clearly that the two diastereoisomers **545**:**546** had been formed in essentially equal amounts. Treatment of this mixture of diastereomers **545** + **546** with KHMDS in CH_2Cl_2 at -78°C resulted in stereoselective elimination to afford the *novel* α,β-unsaturated amide **547** in a disappointing 50% d.e., and the major diastereomer was purified easily *via* chromatography. This poor diastereoselectivity is consistent with that observed previously for other α,β-unsaturated aldehydes. Pertinent ^{1}H NMR spectroscopic details for **547** include the presence of a singlet at δ 1.95 ppm corresponding to the allylic methyl protons at the α-position, whilst the new olefinic proton at the β-position appeared as a singlet at δ 6.66 ppm (Scheme 163). Since the stereogenic centres arising from the *(S)*-citronellal fragment in aldolate **545** and **546**, and hence the corresponding *(E)*-amide

547, were not acidic, and unlikely to racemise, it was assumed that *(E)*-**547** ($[\alpha]_D^{25}$ -72.2, c 0.90, CH_2Cl_2) had been formed with no loss of stereochemical integrity.



Scheme 163

Encouraged by this reaction the boron enolate of *N*-propionyl-oxazolidin-2-one **457** was next treated with *(S)*-citronellal **548** (96% pure), which contains a long chain alkyl group containing a stereogenic centre at its β-position. This reaction once again afforded an inseparable mixture of diastereoisomeric *syn*-aldolates **549**:**550** in a combined yield of 93% yield and in a ratio of 1:1 as measured *via* integration of the singlet resonances of the hydroxyl protons of the two diastereoisomers in the crude ^{1}H NMR spectrum at δ 2.73 and δ 2.80 ppm. This mixture of *syn*-aldolates **549** + **550** was then treated with KHMDS to afford potassium alkoxides that cleanly eliminated to afford *novel* α,β-unsaturated *(E)*-amide **551** in 60% d.e., which was purified *via* chromatography to give *(E)*-amide **551** in 55% yield. The allylic methyl protons of *(E)*-**551** at the α-position appeared as a singlet at δ 1.85 ppm in the ^{1}H NMR spectra, while the olefinic proton at the β-position appeared as a triplet at δ 6.44 ppm. Once again, given the non-acidic nature of the stereocentre of *(S)*-citronellal **548** and *(E)*-amide **551**, it was assumed that it had been formed in enantiopure form, which was substantiated by the observation of a specific rotation of +2.7 (c 2.61, CH_2Cl_2) (Scheme 164).



Scheme 164

It should be noted that the diastereoselectivity observed for the formation of *(E)*-**551** was somewhat disappointing however, when compared with achiral *(E)*-amide **489**, which also contains a long alkyl chain that was formed in 92% d.e. under identical conditions (Figure 47).

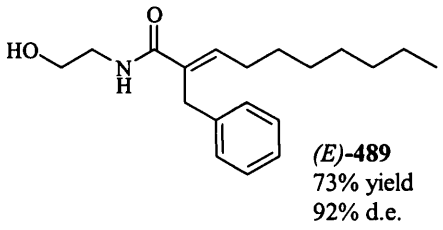
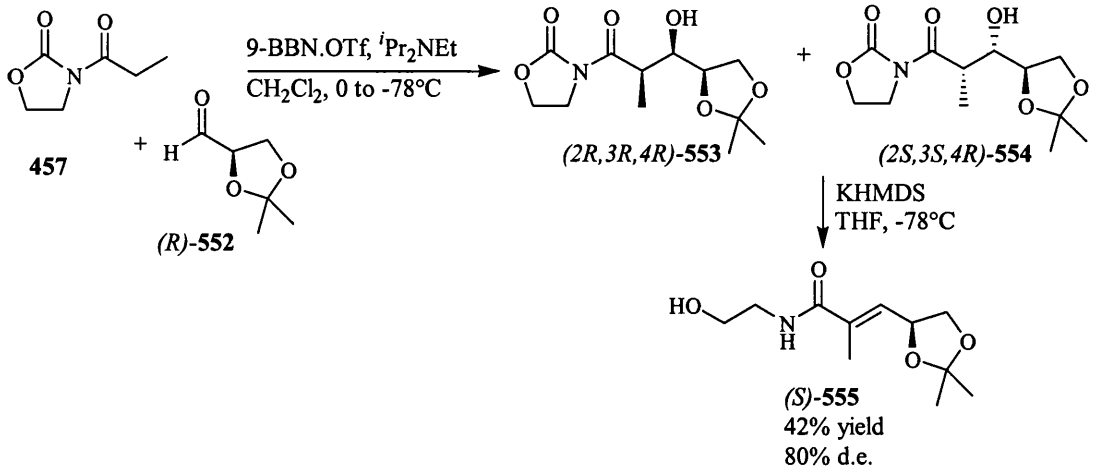


Figure 47

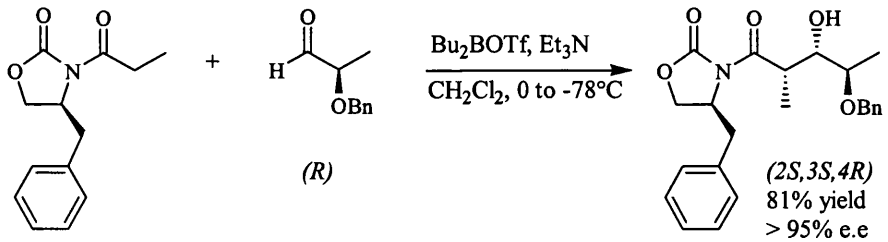
Finally, we proposed to test this elimination methodology using *(R)*-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **552** as an aldehyde substrate that contained a potentially racemisable stereogenic centre at its α-position. Reaction of the boron enolate of *N*-propionyl-oxazolidin-2-one **457** and 1.1 equivalents of aldehyde *(R)*-**552** afforded a mixture of diastereoisomers **553**:**554** which was isolated by chromatography over silica in 58% yield. Once again the complexity of the ^{1}H NMR spectrum of this reaction prevented the diastereomeric excess from being determined. However, analysis of the ^{13}C NMR spectrum revealed that partial kinetic resolution had occurred since a consistent 2:1 enhancement of resonances for one diastereoisomer (unassigned) was observed.[169] Generation of the potassium alkoxide of this mixture of *syn*-aldolates **553** + **554** using KHMDS as base afforded a *novel (E)*-amide in 80% d.e., which after purification *via* chromatography gave pure *(E)*-amide **555** in 42% isolated yield (Scheme 165). The ^{1}H

NMR spectrum of the pure diastereoisomer **555** revealed the allylic methyl group at the α-position as a distinct doublet at 1.93 ppm, J = 1.2 Hz and the olefinic proton at the β-position as a doublet of quartets at 6.25 ppm, J = 8.0, 1.2 Hz.



Scheme 165

The specific rotation of **555** was measured as +4.5 (c 1.54, CH_2Cl_2) indicating that it had been formed in enantiomerically enriched form, but there was some concern that partial racemisation might have occurred during the elimination reaction. It was well known that aldol reaction between the boron enolate of an *N*-acyl-oxazolidin-2-one and chiral aldehydes that contain an acidic α-stereogenic centre occurs with no loss in stereochemical integrity (Scheme 166).[170]



Scheme 166

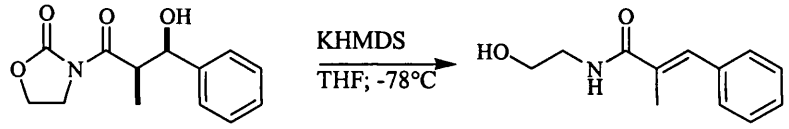
Thus, it was reasoned that if any racemisation had occurred then it would have happened during the subsequent KHMDS mediated elimination reaction of *syn*-aldolates **553:554**. If the structure of the intermediates formed during this elimination reaction are considered, it can be deduced that it is only the final *(E)*-amide product **555** that has the potential to racemise, because it is the only compound that contains a potentially acidic stereocentre due to conjugation to the carbonyl group of the amide functionality. Consequently, it was reasoned that if exposure of a purified sample of *(E)*-amide **555** to KHMDS in THF at -78°C, followed by work-up, resulted in recovery of **555** with an unchanged specific

rotation, then it would be unlikely that racemisation was a problem during the elimination reaction.

Therefore 1.5 equivalents of KHMDS was added to a solution of the *(E)*-amide **555** in THF at –78°C and the reaction left stirring for 1.5 hours. Addition of saturated NH_4Cl_{aq} at –78°C and work up afforded recovered *(E)*-amide **555** in > 95% d.e., whose specific rotation was remeasured in CH_2Cl_2 at +4.8° (c 0.62, CH_2Cl_2), confirming that the elimination reaction conditions were not racemising the stereocentre of *(E)*-amide **555**.

6.2 Elimination of *syn*-aldolates derived from heteroaryl aldehydes

As has been described in the introduction to this thesis, a large amount of effort has been directed towards the stereoselective synthesis of *(E)*-trisubstituted acid derivatives containing aromatic or heteroaryl substituents at their β-position. As described in section 3.1.2 it had been demonstrated that potassium alkoxides of aldolate products containing aromatic groups at the β-position readily eliminated to give α,β-unsaturated amides in a diastereoselective fashion. For example, the reaction of *syn*-aldolate **467** with KHMDS afforded under standard conditions *(E)*-amide **486** in 91% yield and > 95% d.e. (Scheme 167).



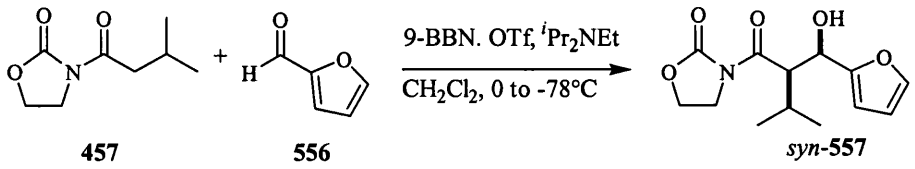
syn-**467**

(E)-**486**
91% yield
> 95% d.e.

Scheme 167

In order to investigate whether similar diastereoselective elimination reactions would occur for *syn*-aldolates derived from heteroarylaldehydes it was decided to investigate the elimination reaction of a *syn*-aldolate derived from a furylaldehyde substrate. It was reasoned that elimination of *syn*-aldolate **557** derived from a furyl fragment with an oxygen substituent at its 2-position would prove to be the most challenging substrate, since problems might arise from coordination of the lone pair of the oxygen atom to the potassium counterion during the elimination process.

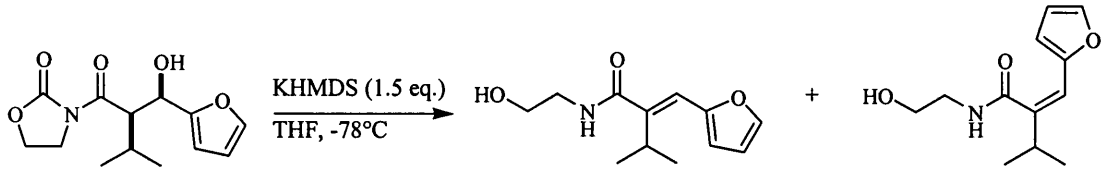
Reaction of 2-furylaldehyde **556** and the boron enolate of *N*-acyl oxazolidin-2-one **457** using our standard protocol afforded *syn*-aldolate **557** in good d.e. but in only 38% yield with most of the mass loss occurring during chromatographic purification of the crude reaction mixture (Scheme 168).



457 556 *syn*-557

Scheme 168

Treatment of the pure aldolate *syn*-**557** with KHMDS resulted in a clean elimination reaction to afford a diastereoisomeric mixture of *(E)*- and *(Z)*-amides **558** and **559** in a very poor ratio of 70:30, which could not be separated by chromatographic purification (Scheme 169). Once again the stereochemistry of *(E)*- and *(Z)*-amides **558** and **559** were assigned in the ^{1}H NMR spectrum by the relative position of the NH peaks, at δ 6.52 ppm and 6.38 ppm respectively.

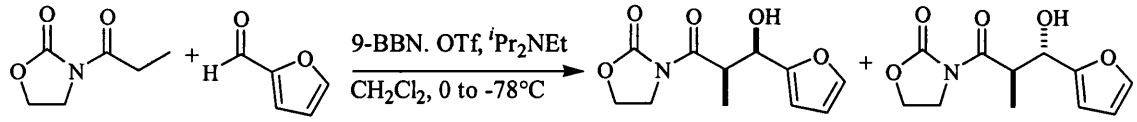


syn-557 70 30

(E)-**558** *(Z)*-**559**

Scheme 169

It was argued that this loss in diastereoselectivity might be a result of steric interactions between the relatively large *iso*propyl group and the furyl substituent in the transition state leading to *(E)*-**558**, and as a consequence the same reaction was investigated using a *syn*-aldolate containing a smaller methyl group at its α-position. Thus, reaction of the boron enolate of *N*-propionyl-oxazolidin-2-one **457** with 2-furaldehyde **556** was carried out to give a mixture of *syn*- and *anti*-aldolate diastereoisomers that were separated after exhaustive chromatography to afford *syn*-aldolate **560** in only a poor 19% yield (and its *anti*-isomer **561** in 4% yield). The products were assigned according to the coupling constants between α-C*H*CH_3 and β-C*H*OH: for the *syn*-isomer, J = 4.5 Hz whilst for the *anti*-isomer J = 8.5Hz (Scheme 170).

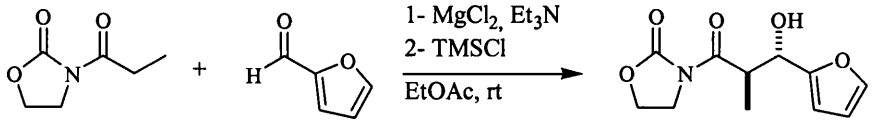


457 556 *syn*-**560** 19% yield *anti*-**561** 4% yield

Scheme 170

Since this aldol reaction had occurred to afford *syn*-aldolate **560** in relatively poor d.e. and very poor yield, it was decided to use the Evans' magnesium enolate procedure to prepare the corresponding *anti*-aldolate **561** since it had already been demonstrated that potassium

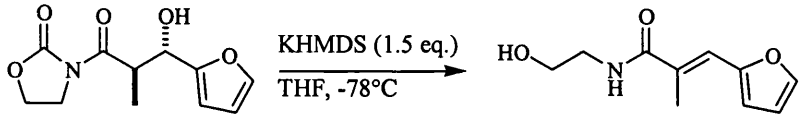
alkoxides of both *syn*- and *anti*-aldolates eliminated to afford *(E)*-α,β-unsaturated amides in essentially the same d.e. Thus, the magnesium enolate of *N*-propionyl-oxazolidin-2-one **457** was reacted with 2-furaldehyde under Evans' conditions to afford *anti*-aldolate **561** in 80% d.e. and 77% isolated yield (Scheme 171).



457 **556** *anti*-**561**
77% yield
80% d.e.

Scheme 171

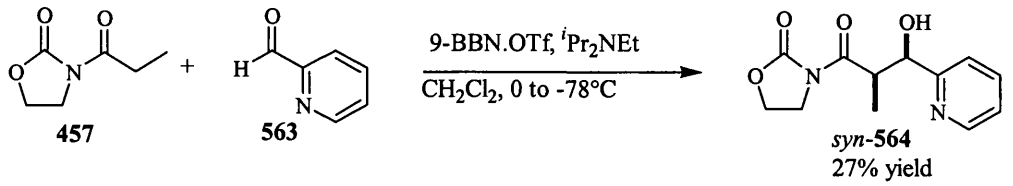
Treatment of *anti*-aldolate **561** with KHMDS in THF at –78°C resulted in a clean elimination reaction to afford *(E)*-α,β-unsaturated amide **562** in >95% d.e. and in 61% yield (Scheme 172). It is clear therefore that the presence of bulky substituents at the α-position of *syn*-aldolate substrates can result in a loss in diastereocontrol in the subsequent KHMDS-mediated elimination reaction.



anti-**561** *(E)*-**562**
61% yield
>95% d.e.

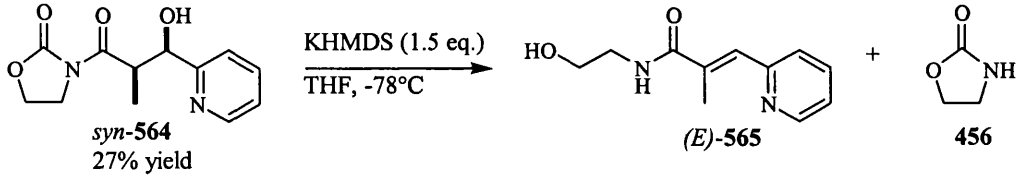
Scheme 172

Having demonstrated that an *anti*-aldolate derived from an oxygen heterocyclic derivative could be successfully eliminated it was next decided to study the elimination of an aldolate substrate derived from 2-pyridine-carboxaldehyde **563**. Thus, reaction of 2-pyridinecarboxaldehyde **563** with the boron enolate of *N*-propionyl-oxazolidin-2-one **457** afforded a crude reaction product containing the desired *syn*-aldolate **564** in good d.e. The recovered yield of the crude product was lower than expected, which in hindsight was due to the protocol employed for work-up: the boron alkoxide was quenched with a phosphate buffer solution (pH 7) which may have allowed partial protonation of the pyridine ring and loss into water. Initial purification through silica gel chromatography was only partially successful, since the product appeared to decompose on silica affording the desired *syn*-aldolate **564** in < 10% yield. Purification of the crude reaction product through a column of alumina was more successful however affording *syn*-aldolate **564** in 27% yield, which was fully characterised (Scheme 173).

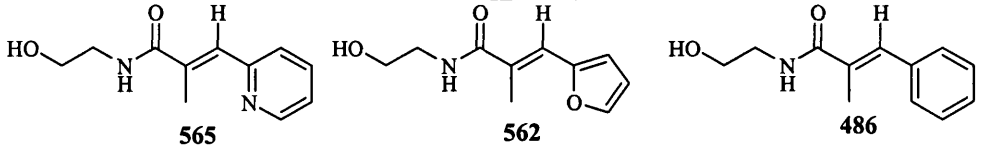


Scheme 173

Unfortunately, attempts to address this yield problem using Evans' alternative magnesium enolate protocol to prepare the corresponding *anti*-aldolate were unsuccessful affording only recovered starting *N*-propionyl-oxazolidin-2-one **457**. Nevertheless, reaction of *syn*-aldolate **564** with KHMDS under standard conditions afforded a crude reaction product, which ^{1}H NMR spectroscopy revealed to be a mixture of *(E)*-α,β-unsaturated amide **565** and the parent oxazolidin-2-one **456**. Chromatographic purification of this mixture of products over silica or alumina was unsuccessful due to the polarity of the products, which appeared to result in decomposition of the desired *(E)*-amide **565**. The mixture was therefore partially characterised as a mixture of *(E)*-amide **565** and oxazolidin-2-one **456** *via* ^{1}H NMR spectroscopy, by subtracting the resonances arising from oxazolidin-2-one **456** (Scheme 174). This partial characterisation of **565** was entirely consistent with the spectroscopic data previously afforded for *(E)*-amides **562** and **486** (Table 27). In hindsight, it is clear that it would have been better to attempt to purify **565** via extraction into acid, however time constraints prevented this from being carried out.



Scheme 174



δ CH_3	2.28	2.17	2.04
δ N*H*	7.02	6.44	6.48
δ C*H*=C	7.29	7.12	7.19

Table 27

It was noteworthy that for the first time in my studies the potassium alkoxide of *syn*-β-hydroxy-*N*-acyloxazolidin-2-one **564** appeared to be collapsing *via* a competing *retro*-aldol pathway with oxazolidin-2-one **456** presumably arising *via* ketene

decomposition of the resulting enolate **566** (Figure 48). It is well known that enolates of *N*-acyl-oxazolidin-2-ones can decompose *via* ketene-like intermediates to afford their parent oxazolidin-2-one **456**,[164,165] whilst pyridine carboxaldehyde **563** was volatile enough to have been removed under reduced pressure during work-up.

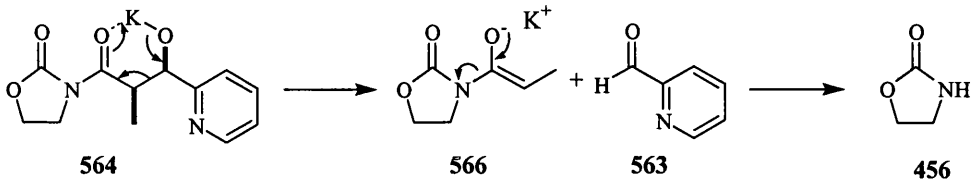
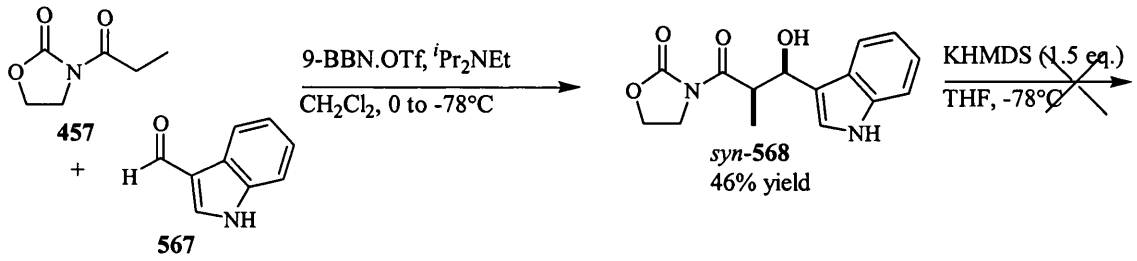


Figure 48

Finally, the use of 3-indole carboxaldehyde **567** as a substrate was explored as part of this investigation into the elimination of heterocylic aldolates. Unfortunately, aldehyde **567** was poorly soluble in most solvents, and in particular CH_2Cl_2, the solvent that was commonly used in our procedure to afford *syn*-aldolates. Therefore, aldehyde **567** was dissolved in dry THF and added to a stirred solution of the boron enolate of *N*-propionyloxazolidin-2-one **457** in CH_2Cl_2. The reaction was stirred at –78°C, then allowed to warm to 0°C to afford *syn*-aldolate **568** in 46% yield after purification *via* recrystallisation from ethyl acetate (Scheme 175). Generation of the potassium alkoxide of *syn*-aldolate **568** afforded a complex untractable mixture which ^{1}H NMR spectroscopy revealed contained at least 6 compounds and as a consequence this experiment was not pursued further.



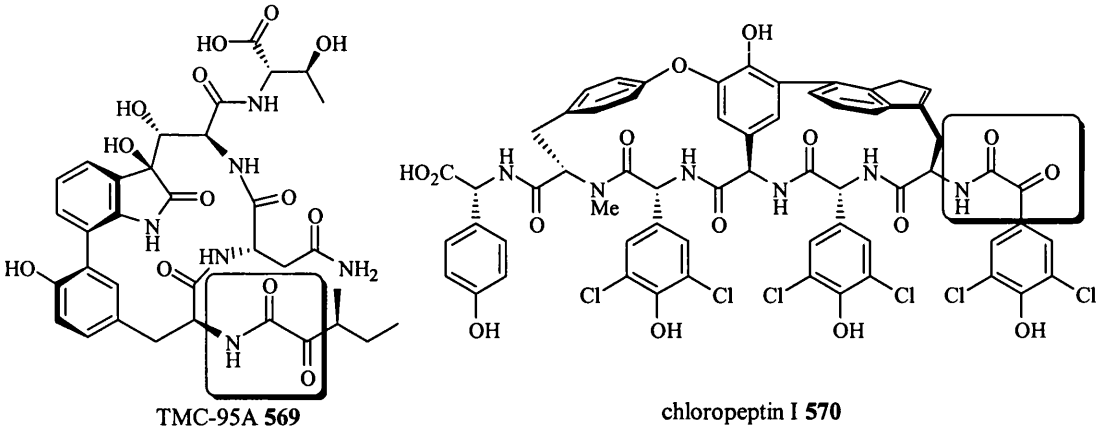
Scheme 175

6.3 Elimination studies of aldolates containing heteroatoms at their α-position

It was next decided to determine whether aldolates that contained heteroatom substituents at their α-position would also undergo stereoselective elimination reactions on treatment with KHMDS.

6.3.1 Synthesis of masked α-keto-amides

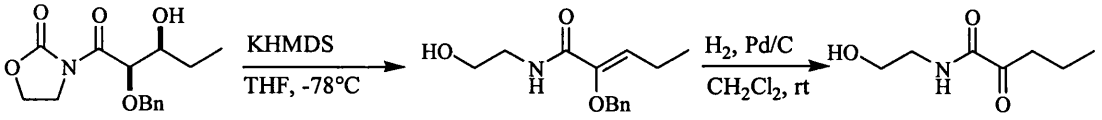
The application of the rearrangement/elimination methodology to α-benzyloxy-aldolate substrates would enable an efficient protocol to be developed for the synthesis of α-keto-acid fragments, that would be of great interest to the synthetic community since 1,2-diketo functionalities are present in peptidic natural products, such as proteasome inhibitor TMC-95A **569**,[171] and anti-HIV agent chloropeptin I **570** (Figure 49).[172]



TMC-95A **569** chloropeptin I **570**

Figure 49

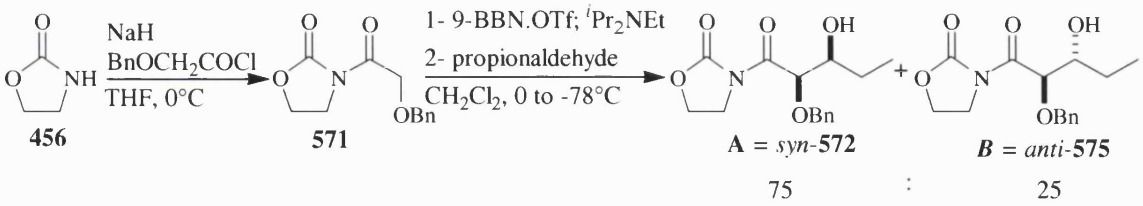
In this regard, it was proposed that treatment of *syn*-aldolate **572** with KHMDS would result in formation of an *(E)*-α,β-unsaturated amide **573** that also contained a benzylic enol-ether fragment. Subsequent hydrogenation of *(E)*-**573** would then remove the benzyl protecting group to cleanly afford the desired *(E)*-α-ketoamide product **574** under mild conditions (Scheme 176).



syn-**572** *(E)*-**573** **574**

Scheme 176

Therefore, reaction of the sodium anion of oxazolidin-2-one **456** with benzyloxyacetylchloride cleanly afforded *N*-acyl-oxazolidin-2-one **571** containing a benzyloxy-substituent at its α-position, which was purified *via* recrystallisation from ethyl acetate in 79% yield. The boron enolate of *N*-acyl oxazolidin-2-one **571** was then generated *via* treatment with 9-BBN-OTf and $^{i}Pr_2NEt$, and reacted with propionaldehyde to afford a mixture of two diastereoisomers **572** and **575** in a poor 50% d.e. (Scheme 177).



Scheme 177

Purification by exhaustive chromatography gave two aldolate products **A** (major) and **B** (minor) in 52 and 10% yield respectively. The coupling constants between β-C*H*OH and α-C*H*OCH$_2$Ph for **A** were J = 2.5 Hz, and for **B** J = 7.0 Hz, and as a consequence they were tentatively assigned as the *syn*-**572** and *anti*-**575** aldolates respectively. The *syn*-geometry of **A** was subsequently confirmed by growing suitable crystals from ethyl acetate and petroleum ether, which were subjected to X-ray crystallographic analysis (Figure 50).

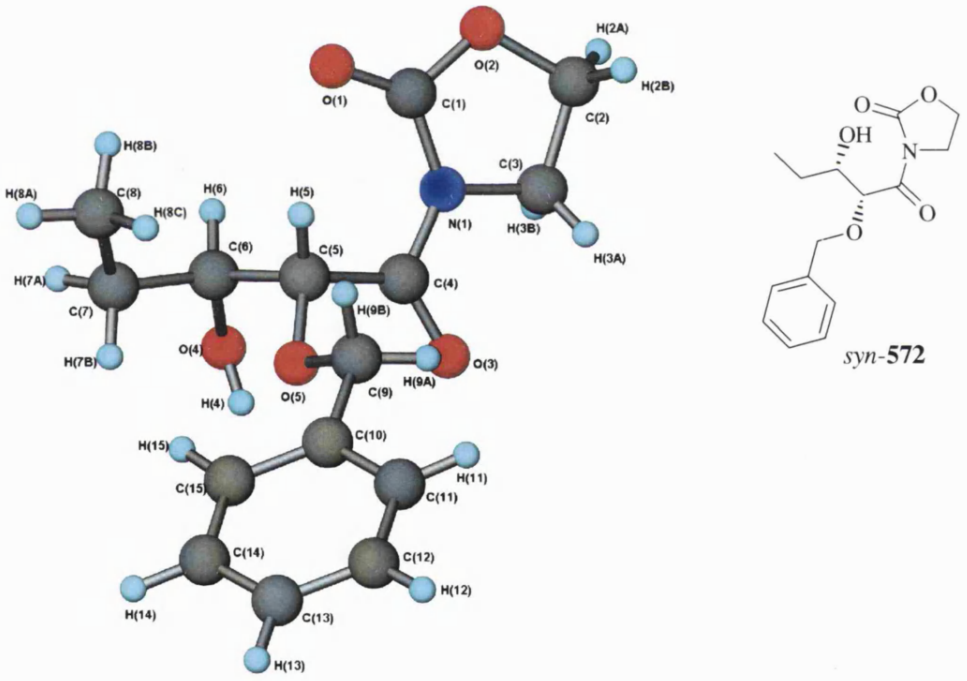
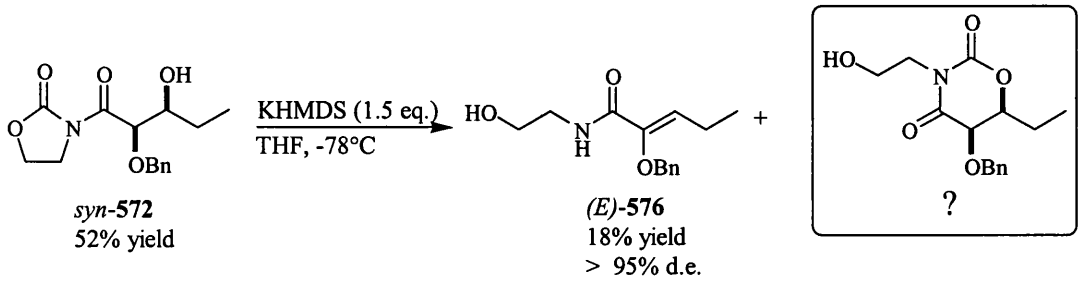


Figure 50. X-ray crystal structure of *syn*-aldolate **572**

The potassium alkoxide of *syn*-aldolate **572** rearranged and eliminated to afford α,β-unsaturated amide *(E)*-**576** in an unoptimised 18% isolated yield after silica gel chromatography (Scheme 178), with the representative olefinic and amidic protons appearing as a triplet at 6.24 ppm and a broad singlet at 6.76 ppm. The loss in mass is at least partly due to a side-reaction that afforded a product whose identity was not

determined, because it could not be found after chromatography, but was tentatively assigned as the *syn*-oxazinane-2,4-dione from analysis of the crude ^{1}H NMR spectrum.

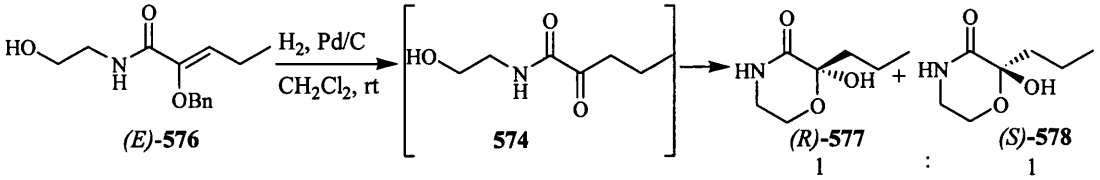


syn-**572**
52% yield

(E)-**576**
18% yield
> 95% d.e.

Scheme 178

Whilst the overall yield of this elimination reaction was clearly unsatisfactory, the benzyl-protected enol-ether **576** was dissolved in CH_2Cl_2 in the presence of a catalytic amount of Pd/C and the reaction mixture stirred under one atmosphere of hydrogen. ^{1}H NMR spectroscopic analysis of the crude reaction mixture did not afford the expected α-keto-amide **574**, but instead revealed the presence of two new products **A** and **B** that had been formed in a ratio of 1:1. Analysis of the ^{1}H NMR spectrum of this mixture of compounds **A** and **B** revealed that **A** displayed resonances with a methyl triplet at δ 0.88 ppm, a sextet at δ 1.39 ppm and a broad singlet (N*H*) at δ 6.97 ppm. These three peak multiplicities were mirrored for unknown compound **B** by a triplet at δ 0.89 ppm, a sextet at δ 1.58 ppm and a broad singlet (N*H*) at δ 7.31 ppm, indicating that these compounds were likely to be structurally related isomers. This assumption was confirmed by thin-layer chromatographic analysis which revealed a single spot by tlc indicating that compounds **A** and **B** were co-eluting. With this data in hand it was concluded that the hydrogenolytic deprotection had been successful to afford the desired α-keto-amide **574** which had then undergone further reaction to afford a mixture of 6-membered hemi-acetals **577** and **578**, *via* intramolecular attack of the ω-hydroxyl group onto the α-keto group. Unsurprisingly, this mixture of hemi-acetals could not be separated *via* chromatography, and were partially characterised as a mixture *via* ^{1}H NMR and ^{13}C NMR spectroscopy and low resolution mass spectrometry (Scheme 179).

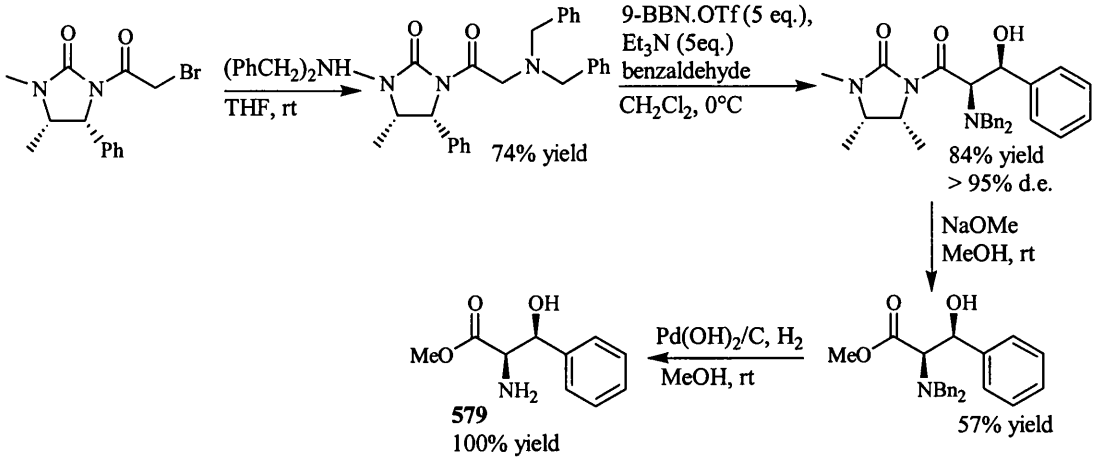


(E)-**576** **574** *(R)*-**577** 1 : 1 *(S)*-**578**

Scheme 179

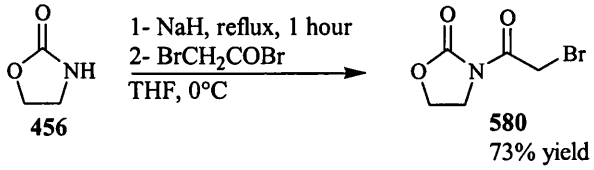
6.3.2 Attempted elimination of α-bromo-aldolates

It was next decided to target the preparation of α-bromo-*syn*-aldolate as a substrate for elimination studies, since it could be employed as a versatile substrate for the preparation of a wide range of other *syn*-aldolates *via* simple displacement of the α-bromo substituent using a range of different nucleophiles. For example, a similar procedure had been employed by Caddick *et al.* for the synthesis of enantiopure α-amino acid **579** according to the strategy described in Scheme 180.[152]



Scheme 180

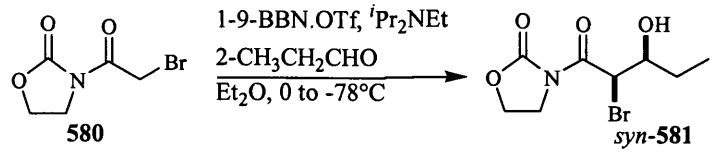
Attempts to prepare α-bromo-*N*-acyl-oxazolidin-2-one **580** *via* treatment of the parent oxazolidin-2-one **456** with NaH followed by addition of α-bromo-acetyl chloride were unsuccessful in my hands. Modification of these reaction conditions in which the parent oxazolidin-2-one **456** was refluxed with excess NaH in THF for two hours, followed by cooling to 0°C, and addition of bromoacetylbromide resulted in formation of the desired *N*-acyloxazolidin-2-one **580** in a good 73% isolated yield (Scheme 181).[173]



Scheme 181

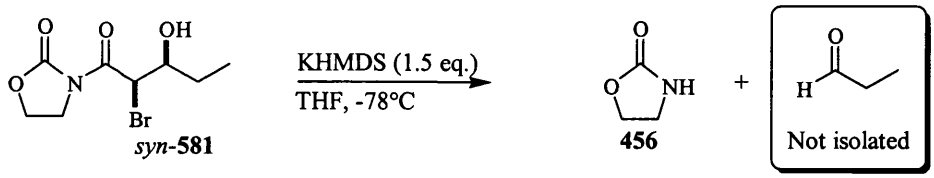
The aldol reaction between α-bromo-*N*-acetyl-oxazolidin-2-one **580** and propionaldehyde was then carried out under standard conditions, to afford the desired *syn*-aldolate **581** in only 19% yield after purification through silica gel chromatography. Indeed, Evans *et al.* had reported previously that reaction of the boron enolate of the parent chiral *N*-chloroacetyloxazolidin-2-one with benzaldehyde in CH_2Cl_2 had also not proceeded to completion, affording a 70:30 mixture of *syn*-aldolate and unreacted starting material.[174] However, the same reaction carried out in Et_2O as solvent had afforded the desired

syn-aldolate in 79% yield, and as a consequence I employed these conditions for reaction to afford *syn*-aldolate **581** in an improved 37% yield (Scheme 182).



Scheme 182

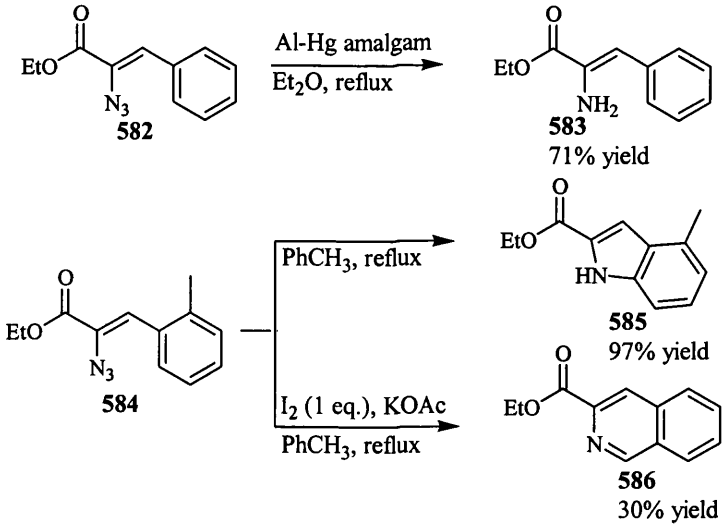
The potassium alkoxide of *syn*-aldolate **581** was generated in the usual manner, which resulted in the formation of the parent oxazolidin-2-one **456** as the only product, thus completely favouring the *retro*-aldol pathway over the E1cB elimination (Scheme 183).



Scheme 183

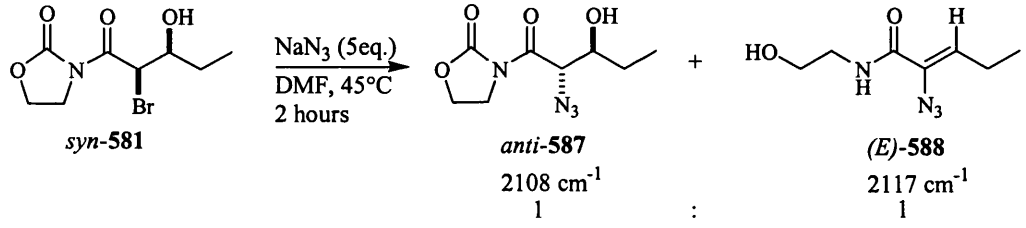
6.3.3 Synthesis of vinyl azides

With α-bromo-*syn*-aldolate **581** in hand I next attempted to displace the α-bromo-substituent with azide, reasoning that this would potentially afford access to α,β-unsaturated amides containing a vinyl-azide fragment, a functionality that had been shown previously to afford good potential for further synthesis. For example, treatment of azidocinnamate **582** with Al-Hg amalgam was shown to afford aminoester **583** in 71% yield,[175] whilst indole **585** and isoquinoline derivative **586** are readily available from decomposition of azidocinnamate **584** (Scheme 184).[176]



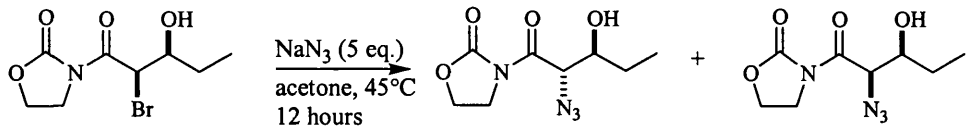
Scheme 184

Treatment of α-bromo-*N*-acyl-oxazolidin-2-one-*syn*-aldolate **581** with a large excess of sodium azide in DMF over a period of 2 hours resulted in the formation of two *novel* products **A** and **B** in a 1:1 ratio, which were separated by chromatography. The ^{1}H NMR spectrum of **A** was very similar to the ^{1}H NMR spectra of *syn*-aldolate **581**, however the doublet resonance corresponding to the CHBr of *syn*-aldolate **581** at 5.63 ppm had been shifted upfield to 4.94 ppm. The infra-red spectra of **A** also revealed the presence of a sharp and strong absorption at 2108 cm^{-1}, characteristic of an azido group and as a consequence product **A** was assigned as the target α-azido-*N*-acyl-oxazolidin-2-one-*anti*-aldolate **587** that had been formed *via* S_N2-type nucleophilic substitution. ^{1}H NMR spectroscopic analysis of product **B** revealed a broad singlet at 6.76 ppm and a triplet at 6.18 ppm, and a strong and sharp absorption in the infra-red spectra at 2117 cm^{-1} for an azide group, that was clearly indicative of formation of *(E)*-α-azido-trisubstituted-α,β-unsaturated amide **588**. The isolation of *(E)*-amide **588** as a product from this reaction is somewhat surprising however, since it implied that sodium azide was functioning as a base to afford the sodium alkoxide of *syn*-aldolate **581**, which had then undergone elimination *via* the usual pathway to afford *(E)*-**588** (Scheme 185).



Scheme 185

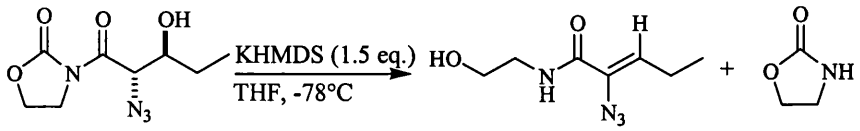
In an attempt to drive this elimination reaction to completion, the reaction was then repeated under the same conditions over a longer 24 hour period, however essentially the same 1:1 ratio of products was obtained from this reaction. However, increasing the temperature of the reaction to 70°C over a period of 12 hours did result in total conversion to the unsaturated *(E)*-amide **588** as the only observable product in the crude ^{1}H NMR spectrum, but only in a low 50% yield due to difficulties associated with its extraction from DMF into organic solvent during aqueous work-up of the reaction. In order to address this isolation problem the azide displacement reaction was repeated using acetone as a solvent instead of DMF from which any *(E)*-amide product would be more easily recoverable. Thus, the reaction of *syn*-aldolate **581** with sodium azide in acetone at reflux afforded cleanly a 85:15 mixture of *anti*- and *syn*-aldolate **587** and **589** in an unoptimised yield of 50% (Scheme 186).



syn-**581** *anti*-**587** 85 *syn*-**589** 15

Scheme 186

Treatment of the α-aza-*anti*-aldolate **587** with KHMDS in THF at -78°C in the usual manner resulted in the formation of the α-aza-α,β-unsaturated amide *(E)*-**588**, and oxazolidin-2-one **456** (from *retro*-aldol pathway) in a ratio of 4:1 (Scheme 186). The mixture was separated *via* chromatography to afford *(E)*-α-aza-amide **588** in 36% isolated yield.



anti-**587** *(E)*-**588** 4 **456** 1

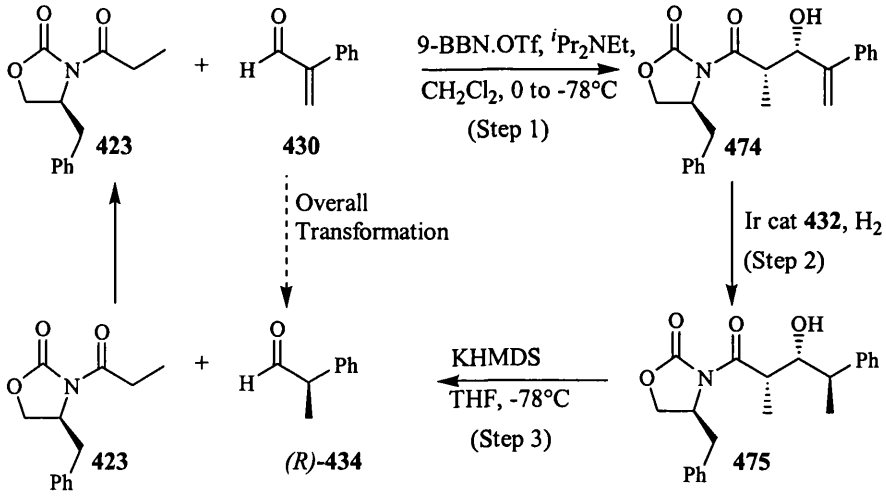
Scheme 187

Conclusion This chapter has described some promising preliminary investigations into the elimination of *N*-acyl-oxazolidin-2-one aldolates derived from chiral aldehydes and heteroaryl aldehydes, as well as aldolates that contain α-heteroatom substituents. Results arising from these investigations clearly reveal that the rearrangement/elimination protocol described has great potential for the synthesis of *(E)*-α,β-unsaturated carboxylic acid derivatives of use in natural product synthesis, medicinal chemistry and organic synthesis and. Further investigations to optimise both the yields and range of substrates employed in these eliminations reactions are currently underway within the SDB research group.

CHAPTER 7. Optimising the *retro*-Aldol Reaction for Chiral *N*-acyl-oxazolidin-2-one-*syn*-Aldolates

7.1 Introduction

Whilst the decision to employ achiral *N*-acyl-oxazolidin-2-one-*syn*-aldolates had been fruitful, resulting in the discovery of a *novel* elimination reaction, if the original concept of employing a chiral auxiliary in a *novel* manner was to be realised then conditions that would result in a facile *retro*-aldol reaction (Scheme 131, Step 3) still needed to be developed. In the preceding chapters there was clearly evidence that elimination of certain aldolate substrates to afford *(E)*-amides had been accompanied by the formation of products arising from a competing *retro*-aldol reaction. It was therefore necessary to find conditions or substrates (or both) that would efficiently repress the elimination pathway, which in turn would enable the *retro*-aldol pathway to predominate.



Scheme 131

7.2 Exploring the reactivity of alkoxides of *N*-acyl-oxazolidin-2-one-*syn*-aldolates containing an α-aryl group

It was reasoned that elimination of *syn*-aldolate **590** derived from *N*-phenylacetyl-oxazolidin-2-one **459** might favour the *retro*-aldol pathway, since the resultant enolate would be stabilised by the capacity of the α-phenyl substituent to afford extra conjugation (Figure 51).

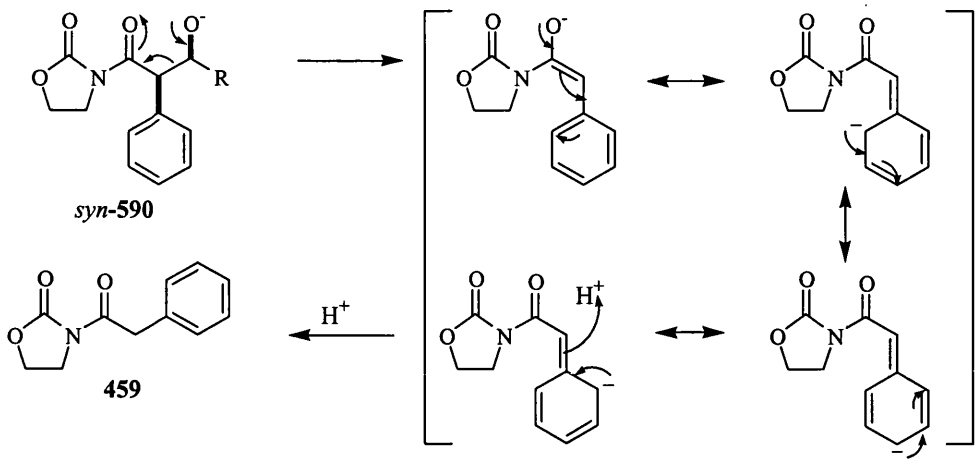
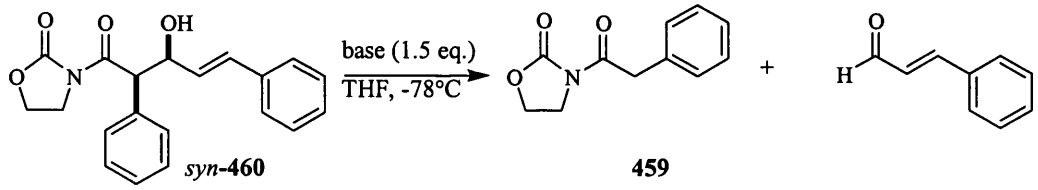


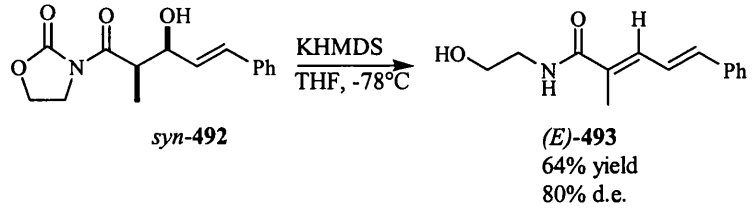
Figure 51

Indeed, to my delight, treatment of *syn*-aldolate **460** with a series of alkali metal bases (LHMDS, KHMDS and NaHMDS) in THF at –78°C resulted in the desired *retro*-aldol reaction to afford a mixture of *N*-phenylacetyloxazolidin-2-one **459** and *trans*-cinnamaldehyde. Comparison of the crude ^{1}H NMR spectra indicated that deprotonation of *syn*-aldolate **460** with KHMDS had afforded the cleanest reaction product with the resultant potassium alkoxide cleanly undergoing a *retro*-aldol reaction to afford the best overall yield of *N*-phenylacetyloxazolidin-2-one **459**. Reaction of **460** with LHMDS gave a more complex mixture of products, whilst reaction with NaHMDS afforded some *(E)*-amide product *via* the elimination pathway (Scheme 188).



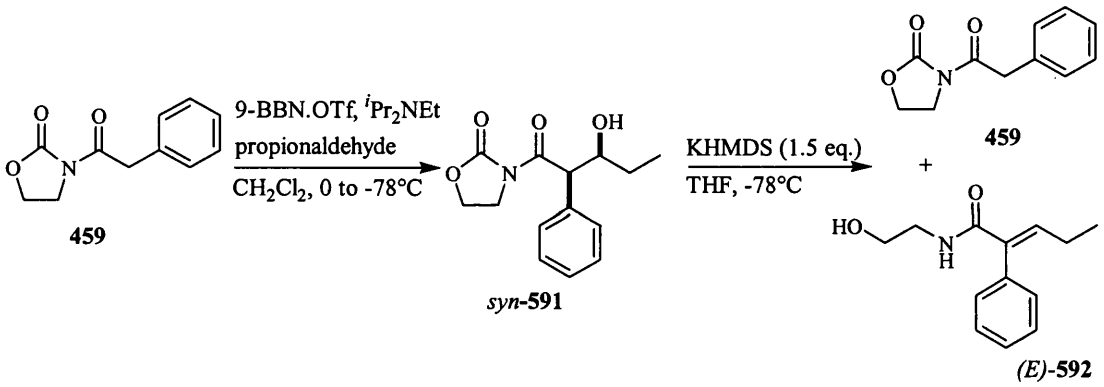
Scheme 188

It should be noted that the observed *retro*-aldol reaction for *syn*-aldolate **460** containing an α-phenyl group is in direct contrast to *syn*-aldolate **492**, that contains an α-methyl group, which I had shown previously had undergone a clean elimination reaction to afford *(E)*-**493** (Scheme 189).



Scheme 189

Whilst these results clearly indicated that potassium alkoxides of an *N*-phenylacetyl-*syn*-aldolate derived from an α,β-unsaturated aldehyde had undergone a clean *retro*-aldol reaction, it was still necessary for our chiral auxiliary approach to develop conditions that would enable *syn*-aldolates derived from saturated aldehydes to undergo the same reaction. Since electronic factors were clearly important in determining whether the alkoxides of *syn*-aldolates underwent elimination or *retro*-aldol reaction, deprotonation of a saturated *syn*-aldolate **591** containing a phenyl substituent at its α-position was next investigated. Thus, the *syn*-aldolate **591** derived from *N*-phenylacetyl-oxazolidin-2-one **459** and propionaldehyde was prepared using 9-BBN.OTf in the usual manner in a poor 37% yield. Treatment of this *syn*-aldolate **591** with KHMDS in THF at -78°C resulted in the formation of a crude reaction product which ^{1}H NMR spectroscopic analysis revealed contained *(E)*-amide **592** arising from an elimination reaction in >95% d.e., and *N*-phenylacetyl-oxazolidin-2-one **459** as a product of the *retro*-aldol reaction, in a ratio of 2:1. The crude reaction mixture was purified to homogeneity to afford *(E)*-amide **592** in 47% yield, which was fully characterised (Scheme 190).

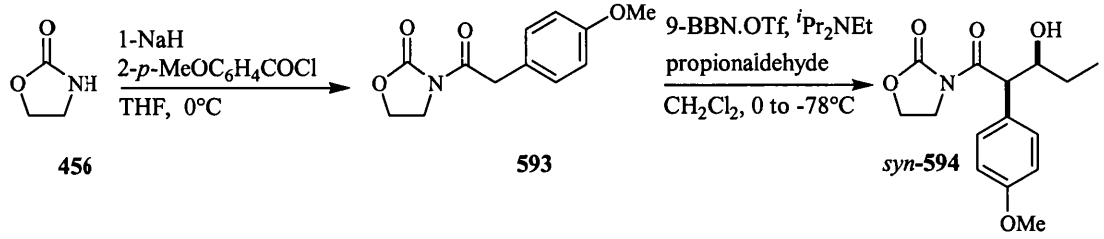


Scheme 190

In order to confirm that the introduction of a phenyl substituent at the α-position of the *syn*-aldolate **460** and **591** was indeed responsible for the increase in the amount of *N*-phenylacetyloxazolidin-2-one **459** arising from the *retro*-aldol pathway, a *syn*-aldolate substrate containing a *para*-methoxy substituent at its α-position was next prepared. It was reasoned that this class of aldolate substrate should afford more *(E)*-amide product arising from the elimination pathway, because the enolate of *N*-*p*-methoxyphenyl-oxazolidin-2-one **593** would be destabilised by the electron rich *para*-methoxy substituent, resulting in the *retro*-aldol pathway being disfavoured.

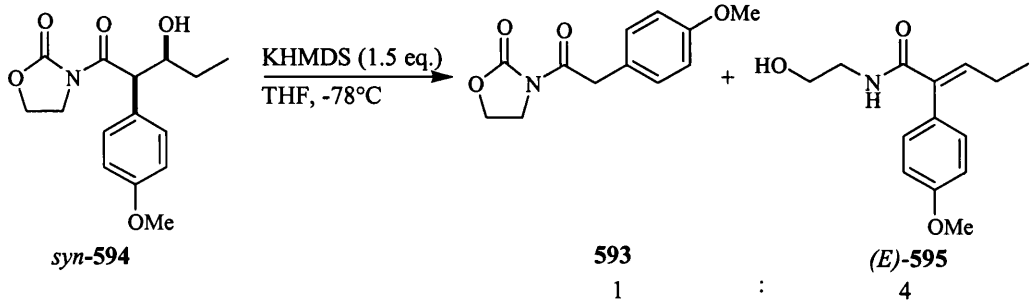
Acylation of the parent oxazolidin-2-one **456** with 4-methoxyphenylacetylchloride proved to be quite challenging, since reaction with the lithium salt of oxazolidin-2-one **456** in THF under standard conditions gave no product. Matsumura *et al.* had described previously that

deprotonation of oxazolidin-2-one with sodium hydride in THF at 0°C, followed by addition of an acid chloride had afforded good yields of *N*-acyl-oxazolidin-2-ones.[177] Thus, under these conditions the desired *N*-acyloxazolidin-2-one **593** was successfully prepared in 69% yield. With *N*-*p*-methoxyphenylacetyl-oxazolidin-2-one **593** in hand its boron enolate was reacted with propionaldehyde under standard conditions, to afford the desired *syn*-aldolate **594** in 77% yield (Scheme 191).



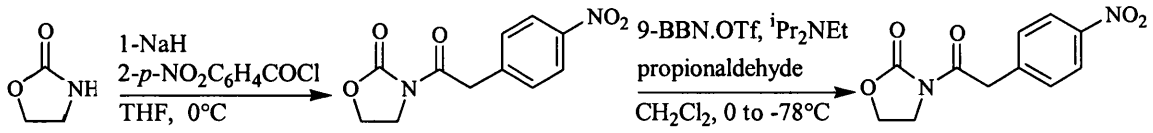
Scheme 191

Treatment of *syn*-aldolate **594** with KHMDS in THF at -78°C resulted in a crude reaction product which ^{1}H NMR spectroscopic analysis revealed contained *(E)*-amide **595** in 75% d.e. and *N*-*p*-methoxyphenyl-oxazolidin-2-one **593** in a ratio of 4:1. *(E)*-amide **595** was subsequently purified to homogeneity *via* chromatography and fully characterised in 39% yield (Scheme 192). Thus, the argument that electronic factors were important in determining the ratio of products arising from the competing elimination/*retro*-aldol reaction appeared to be a valid one, since α-*p*-methoxybenzyl-*syn*-aldolate **594** had afforded less *retro*-aldol product **593** than the corresponding α-phenyl-*syn*-aldolate **591** as predicted by the enolate stabilisation argument.



Scheme 192

In an attempt to confirm this theory, it was proposed to carry out studies on the alkoxide of a *syn*-aldolate derived from α-*p*-nitrophenylacetyl-oxazolidin-2-one **596**, since the presence of the highly electron deficient nitro-aryl group would add additional stabilisation to the enolate arising from the *retro*-aldol pathway. However, all attempts to prepare the desired *syn*-aldolate substrate under standard conditions using 9-BBN.OTf as Lewis acid were unsuccessful, affording only starting material **596** in each case (Scheme 193).

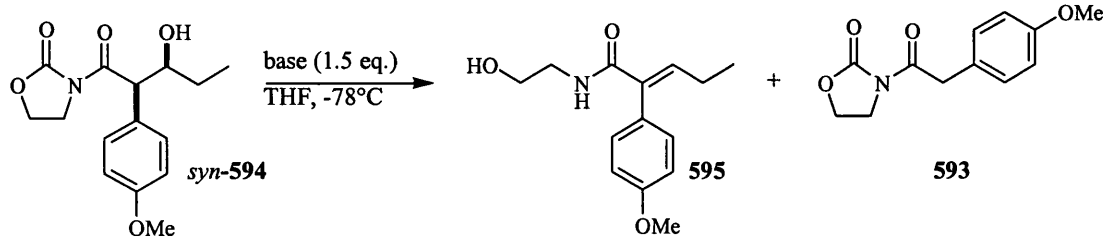


456 596 596

Scheme 193

7.3 Investigating what effect changing the base used for deprotonation of *syn*-aldolate substrates has on the outcome of the reaction

Since it was possible that the ratio of products arising from the elimination/*retro*-aldol pathway might be affected by the nature of the base used for deprotonation of the *syn*-aldolate the effect of changing the nature of the base in this reaction was next investigated. Reaction of the lithium alkoxide of *syn*-aldolate **594** resulted in a crude reaction product that contained a number of unknown compounds (<10%), as well as unsaturated *(E)*-amide **595** and *N-p*-methoxyphenyl-oxazolidin-2-one **593** in a ratio of 9:1. Alternatively, reaction of *syn*-aldolate **594** with NaHMDS in THF at -78°C gave a crude reaction product containing *(E)*-amide **595** and *N-p*-methoxyphenylacetyl-oxazolidin-2-one **593** in a ratio of 77:23 similar to that previously observed for KHMDS. Attempts to screen alternative bases for elimination were initially unsuccessful, since treatment of *syn*-aldolate **594** with sodium hydride or potassium ^{tert}-butoxide in THF at -78°C resulted in no reaction, with starting material being recovered in each case. Repeating these reactions at 0°C did result in reaction of *syn*-aldolate **594** however, with sodium hydride affording products **595**:**593** arising from the elimination/*retro*-aldol pathway in a ratio of 67:33, whilst reaction with potassium ^{tert}-butoxide resulted in the same mixture in a ratio of 80:20 (Scheme 194, Table 28). Thus, whilst these results clearly indicated that the ratio of products arising from the elimination/*retro*-aldol reaction could be 'fine-tuned' by varying the base, it appeared unlikely that simply changing the nature of the base would be sufficient to result in a reversal in the reaction manifold so that the *retro*-aldol reaction would dominate over the elimination reaction.



syn-**594** **595** **593**

Scheme 194

	base	temperature	Ratio 595:593	% d.e. of *(E)*-amide 595
1	KHMDS	-78°C	80:20	75
2	LHMDS	-78°C	90:10[a]	78
3	NaHMDS	-78°C	77:23	60
4	NaH	-78°C	-	-
5	NaH	0°C	67:33[b]	68
6	^{t}BuOK	-78°C	-	-
7	^{t}BuOK	0°C	80:20[b]	72

[a] Complex mixture with more than two products; [b] Under the reaction conditions *N*-acyl oxazolidin-2-one **595** decomposed to the parent oxazolidin-2-one **456**.
Table 28

7.4 Studying the reactivity of the alkoxides of chiral-*N*-acyl-oxazolidin-2-ones

These studies had clearly demonstrated that potassium alkoxides of *syn*-aldolates derived from *achiral N*-acyl-oxazolidin-2-ones could react *via* competing elimination/*retro*-aldol pathways, and that the introduction of an aryl group at the α-position of the aldolate maximised the potential for formation of products arising from the *retro*-aldol pathway. It was therefore decided to explore the reactivity of alkoxides of chiral *syn*-aldolates derived from *(S)*-4-benzyl-oxazolidin-2-one **530**. In this regard it was reasoned that elimination of the alkoxide of this type of chiral *syn*-aldolate **597** to form *(E)*-amides **599** would be less likely than for the corresponding elimination of achiral *syn*-aldolates, because introduction of a chiral substituent at the 4-position would help to block intramolecular attack of the β-alkoxide at the carbonyl of the oxazolidin-2-one fragment. This, in turn would suppress the formation of the oxazinane-2,4-dione intermediate **598**, which was necessary for the unwanted elimination pathway to occur (Figure 52).

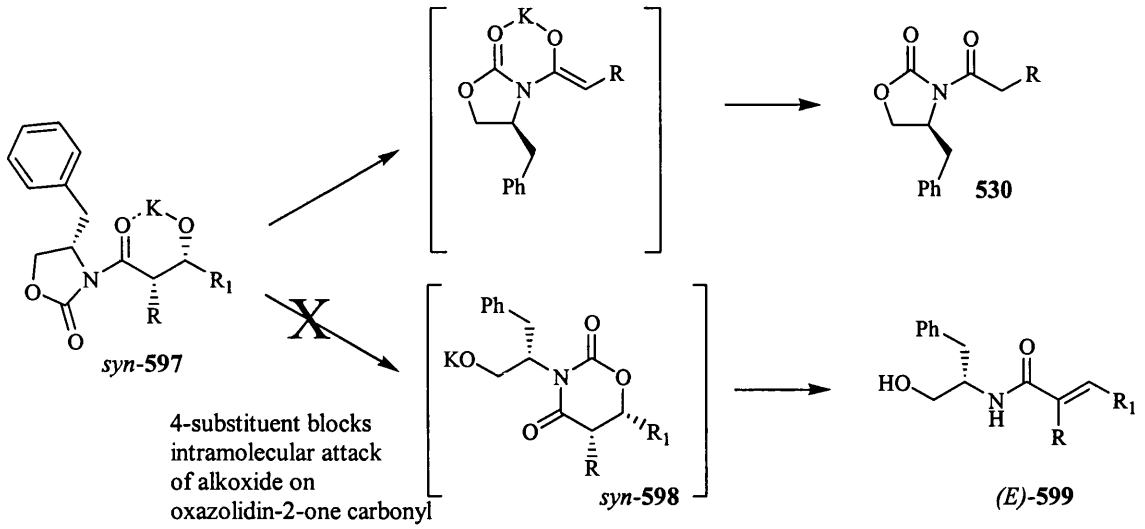
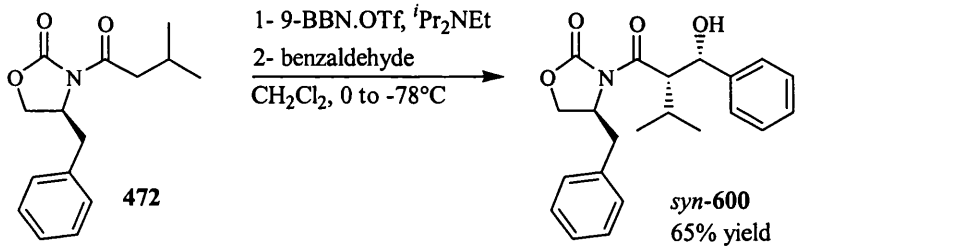


Figure 52

7.4.1 Synthesis of chiral *N*-acyl-oxazolidin-2-one-*syn*-aldolates

Soon after optimising the formation of achiral aldolates I had shown that the 9-BBN triflate methodology was suitable for the formation of chiral aldolates **473** and **440** in an enantioselective fashion (see section 2.2.6.2). Reaction of the boron enolate of chiral *N*-acyl-oxazolidin-2-one **472** with benzaldehyde was also carried out to afford *syn*-aldolate **600** in 65% yield and > 95% d.e. (Scheme 195). The characterisation of *syn*-aldolate **600** was consistent with spectroscopic data of previously prepared and fully characterised *syn*-aldolates **473** and **440** (Figure 53).



Scheme 195

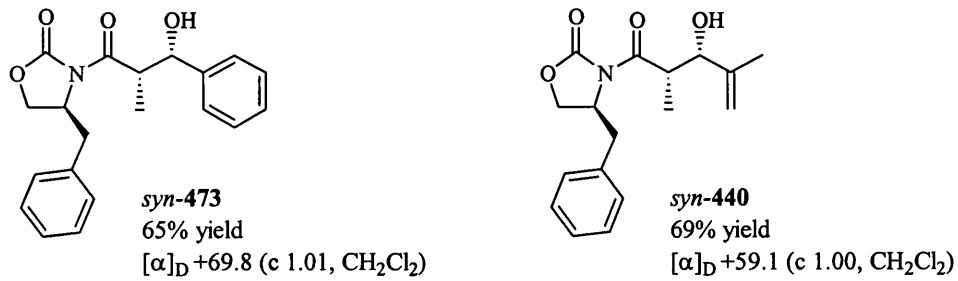
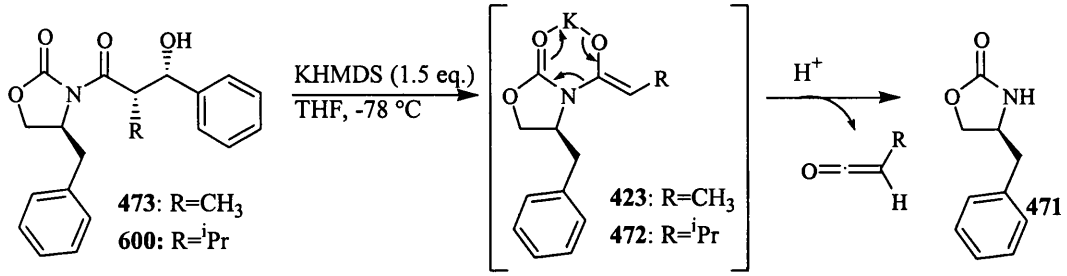


Figure 53

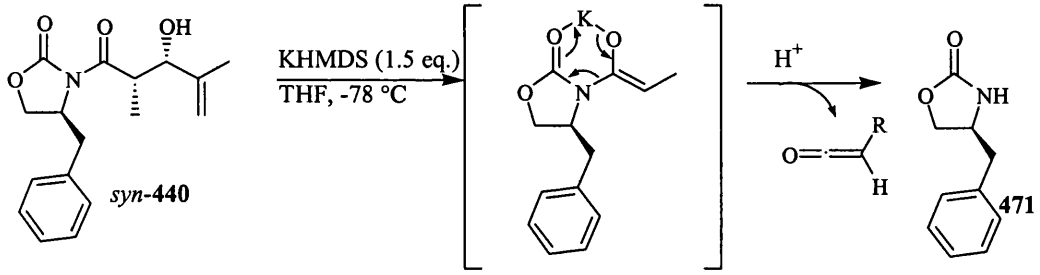
7.4.2 Alkoxides of chiral *N*-acyl-oxazolidin-2-one-*syn*-aldolates undergo clean *retro*-aldol reaction

Treatment of *syn*-aldolates **473** and **600** with KHMDS in THF at -78°C both resulted in a clean reaction to afford the parent 4-benzyl-oxazolidin-2-one **471** and benzaldehyde, with no evidence of any of the corresponding *(E)*-amide product having been formed. It was reasoned therefore that the potassium alkoxides of both *syn*-aldolates **473** and **600** had undergone clean *retro*-aldol reaction to afford their corresponding unstable enolates **423** and **472** (and benzaldehyde) that had decomposed *in situ via* a *retro*-ketene like mechanism to afford the parent oxazolidin-2-one **471** (Scheme 196).



Scheme 196

It was demonstrated earlier in this chapter that alkoxides of achiral *N*-acyl-oxazolidin-2-ones *syn*-aldolate **460** containing γ,δ-unsaturation in the achiral series had collapsed *via* a *retro*-aldol pathway. Likewise generation of the potassium alkoxide of chiral *syn*-aldolate **440** resulted in a clean *retro*-aldol reaction affording the parent 4-benzyloxazolidin-2-one **471** (Scheme 197).

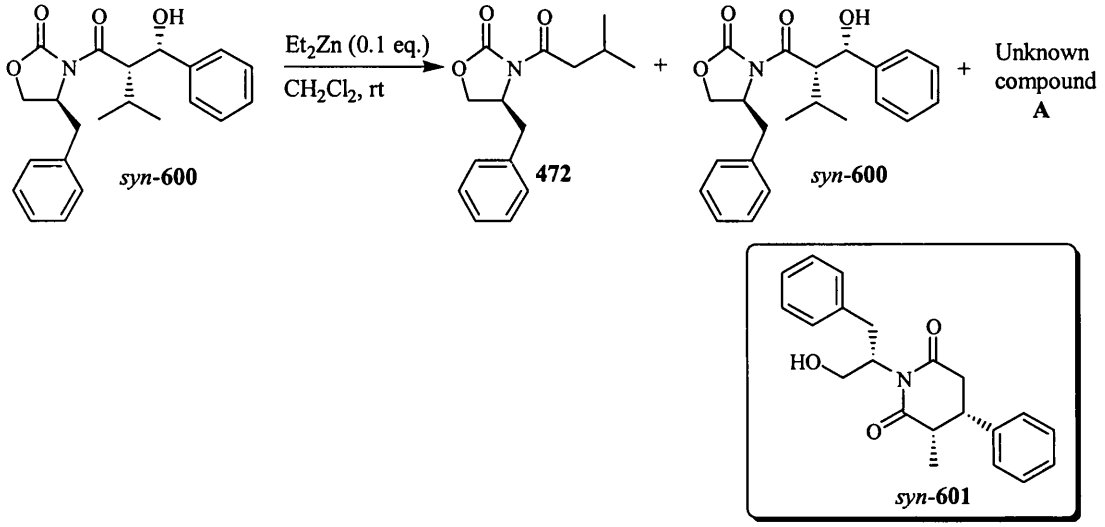


Scheme 197

7.4.3 Attempted rearrangement of chiral *syn*-aldolates to afford chiral oxazinane-2,4- using diethylzinc as base

These results had demonstrated that the presence of the chiral substituent at C4 of the oxazolidin-2-one fragment had suppressed intramolecular cyclisation/elimination reaction of the potassium enolates of a range of chiral *syn*-aldolates. Consequently, I investigated whether a rearranged chiral oxazinane-2,4-dione **601** could be formed *via* treatment of *syn*-aldolate **600** with Et_2Zn. Carrying out this reaction in the usual manner, treatment of

the *syn*-aldolate **600** with diethylzinc in THF, resulted in formation of a crude reaction product, that ^{1}H NMR spectroscopic analysis revealed contained *N*-acyl-oxazolidin-2-one **472**, *syn*-aldolate **600**, and one major unidentified compound **A** as the major product (Scheme 198).



Scheme 198

Exhaustive chromatographic purification of this reaction enabled the unknown product **A** to be isolated in a low 40% yield, which was fully characterised in the usual manner. Examination of the spectroscopic data of **A** led me to propose a structure that was consistent with the formation of a new *N*-acyl-oxazolidin-2-one aldolate diastereoisomer, but *not* with the formation of an oxazinane-2,4-dione **601**. The primary piece of evidence that enabled the oxazinane-2,4-dione skeleton to be discounted was the observed doublet between the β-C-H and the OH of J = 9.5 Hz which was consistent with the formation of an aldolate, but not with the structure of the corresponding oxazinane-2,4-dione *syn*-**601** skeleton which had been shown previously to afford distinctive resonances as either a triplet, or broad singlet. Close examination of the ^{1}H NMR spectrum of **A** also revealed a coupling constant between α-H and the β-H of J = 4.5 Hz, which was consistent with the formation of an *anti*-aldolate structure, since the corresponding coupling constant for the *syn*-aldolate starting material **600** was J = 8.5 Hz. I was therefore left with a choice of two *anti*-aldolates **603** and **604** for the structure of **A** (Figure 54).

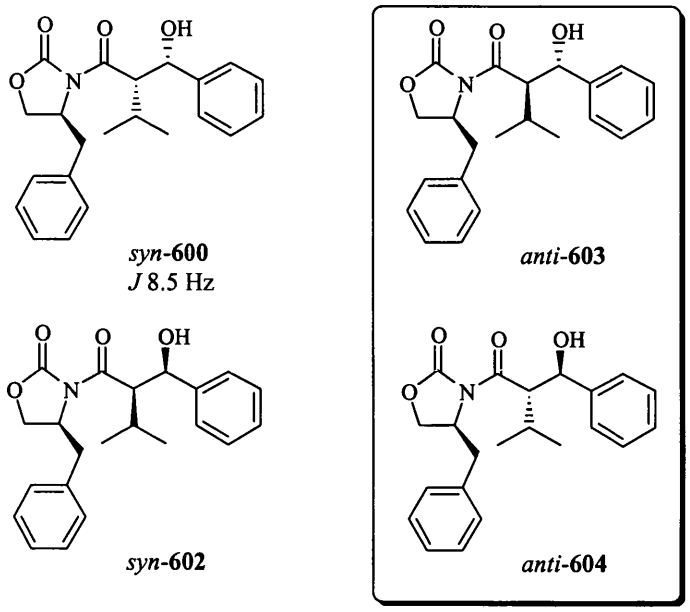
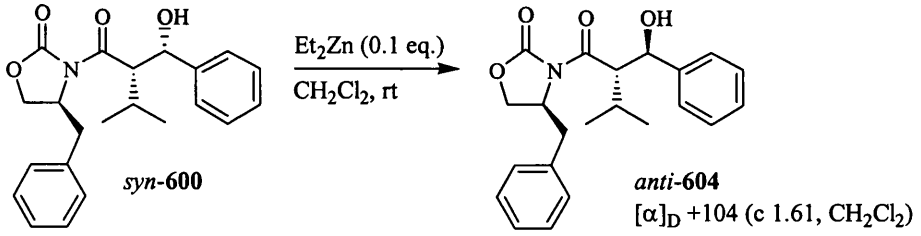


Figure 54

Of the two anti-aldolates, *anti*-**603** had been prepared previously by Evans *et al.*, however there was no spectroscopic data published in the literature.[154] After contacting Professor Evans by personal correspondence, I obtained the unpublished spectroscopic data for his *anti*-aldolate **603**, which on comparison was clearly different from that of product **A**. Thus, by a process of elimination, the structure of the unknown compound **A** was assigned as *anti*-aldolate **604** (Scheme 199).



Scheme 199

It was clear therefore that the presence of the benzyl substituent at the 4-position of the chiral oxazolidin-2-one *syn*-aldolate **600** was sufficient to 'shut-down' the intramolecular rearrangement pathway to afford oxazinane-2,4-dione **601**. It appears therefore that equilibration of the zinc alkoxide of syn-aldolate **600** to its corresponding *anti*-aldolate **604** must have occurred *via retro*-aldol cleavage to afford a zinc enolate **605**, which then undergoes reversible reaction with benzaldehyde to afford the *anti*-aldolate **604** as the major product, presumably under thermodynamic control (Figure 55).

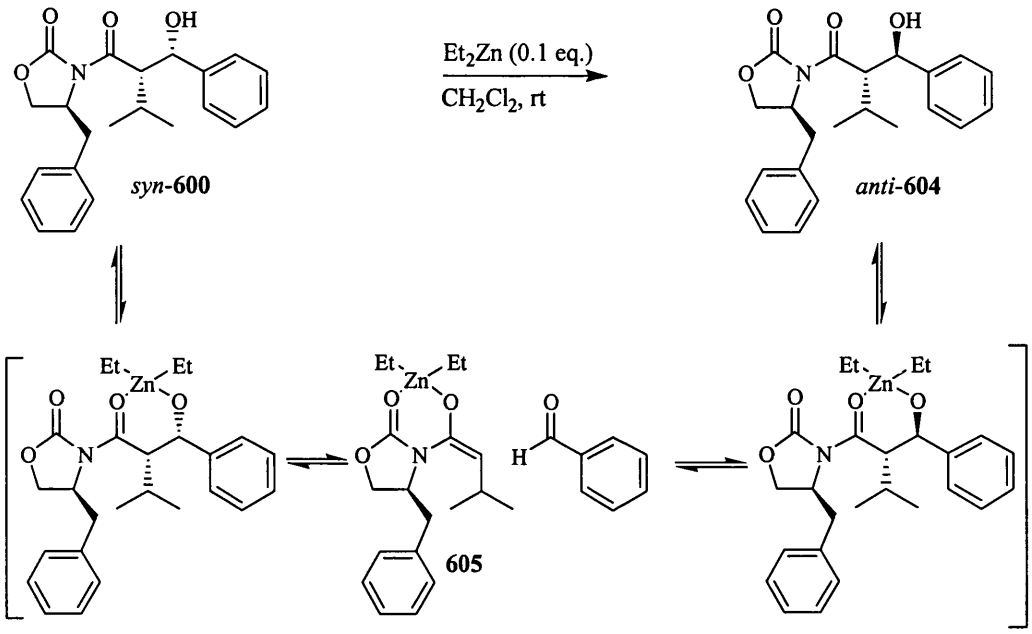
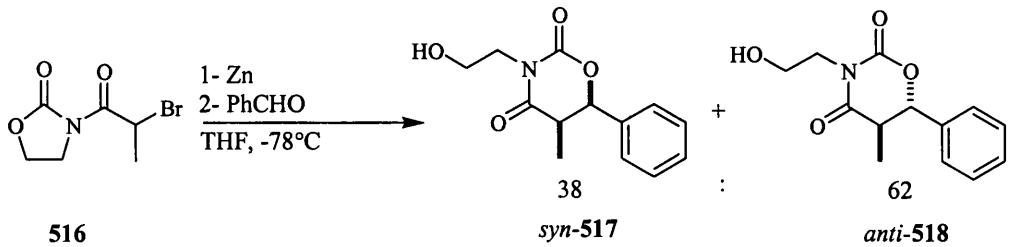


Figure 55

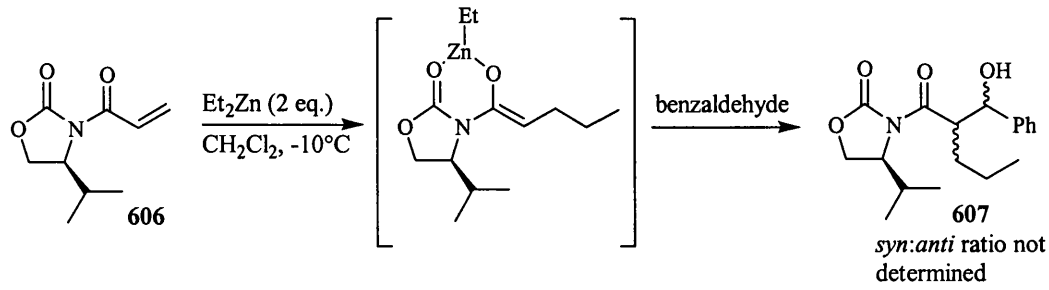
There are three pieces of evidence in support of this reversible *retro*-aldol/aldol mechanism to explain the epimerisation of the β-stereocentre of *syn*-aldolate **600**. Firstly, the corresponding *N*-phenyl-oxazolidin-2-one **472** was identified as a product of this reaction, the enolate **605** of which would be an intermediate on this reversible *retro*-aldol/aldol reaction pathway. Secondly, Ito *et al.* had shown that reaction of the zinc enolate of *N*-acyl-oxazolidin-2-one **516** with benzaldehyde afforded a mixture of *anti*-oxazinane-2,4-dione **518** and *syn*-oxazinane-2,4-dione **517** as products, with the *anti*-diastereoisomer **518** having been formed as the major diastereoisomer (Scheme 149).[153] Since these oxazinane-2,4-diones must have been formed *via* rearrangement of their corresponding *anti*- and *syn*-aldolates, it appears that zinc enolates of *N*-acyl-oxazolidin-2-ones preferentially afford *anti*-aldolates.



Scheme 149

Finally, Bertrand *et al.* prepared a zinc enolate from the reaction of chiral *N*-enoyloxazolidin-2-one **606** with Et_2Zn, which on reaction with benzaldehyde gave a

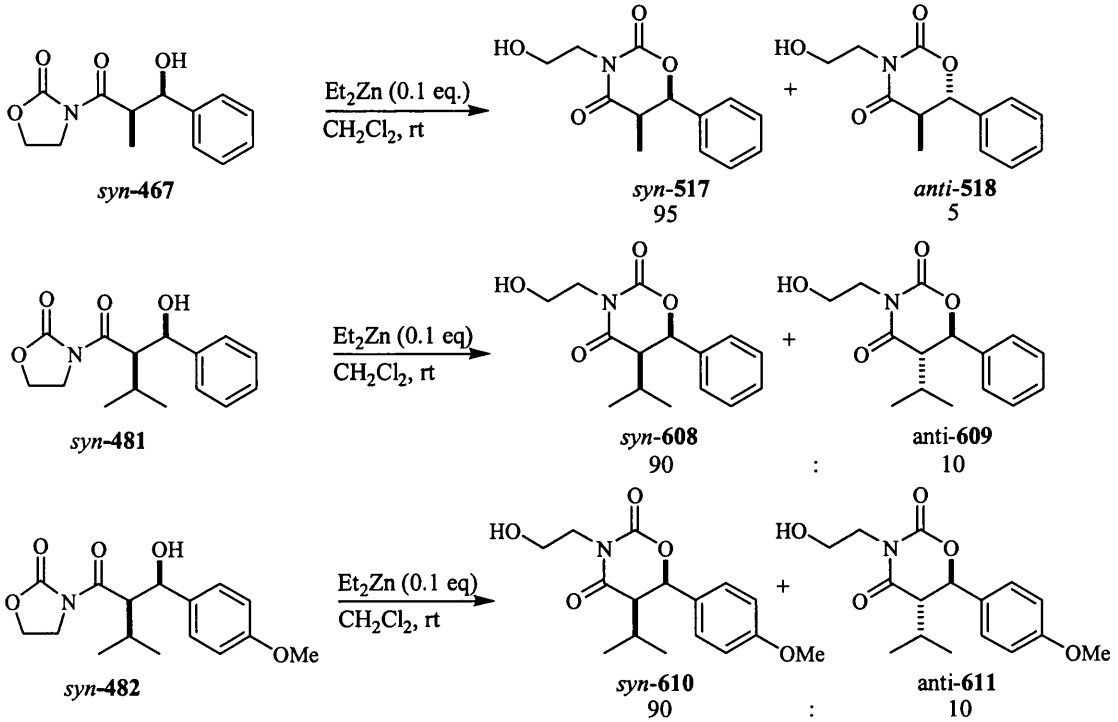
diastereomeric mixture of aldolates **607**, thereby demonstrating that zinc enolates readily afford aldolate products (Scheme 200).[178]



Scheme 200

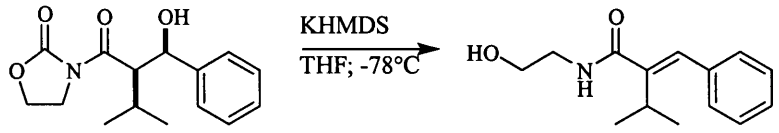
7.4.4 Stereochemical leakage in the rearrangement of achiral β-aryl-*syn*-aldolates

In parallel to this work, and following the study of the mechanism and the isolation of oxazinanediones a series of achiral *syn*-β-arylaldolates were treated with a catalytic amount of diethylzinc in CH_2Cl_2 at room temperature. Unlike the previous achiral substrates, which afforded the corresponding oxazinanediones in high d.e. the zinc alkoxides of *syn*-aldolates **467**, **481** and **482** afforded *syn*-oxazinanediones **517**, **608** and **610** in the presence of significant amounts of the corresponding *anti*-isomers **518**, **609** and **611**. The *syn*-oxazinanediones **608** and **610** were purified through flash chromatography and fully characterised, COSY correlation revealing the characteristic coupling between O*H* and C*H*$_2$O (Scheme 201).



Scheme 201

This study revealed a clear discrepancy with the results obtained previously for the KHMDS-mediated elimination of *syn*-**481**, which had afforded *(E)*-amide **487** in 92% d.e. (Scheme 202).

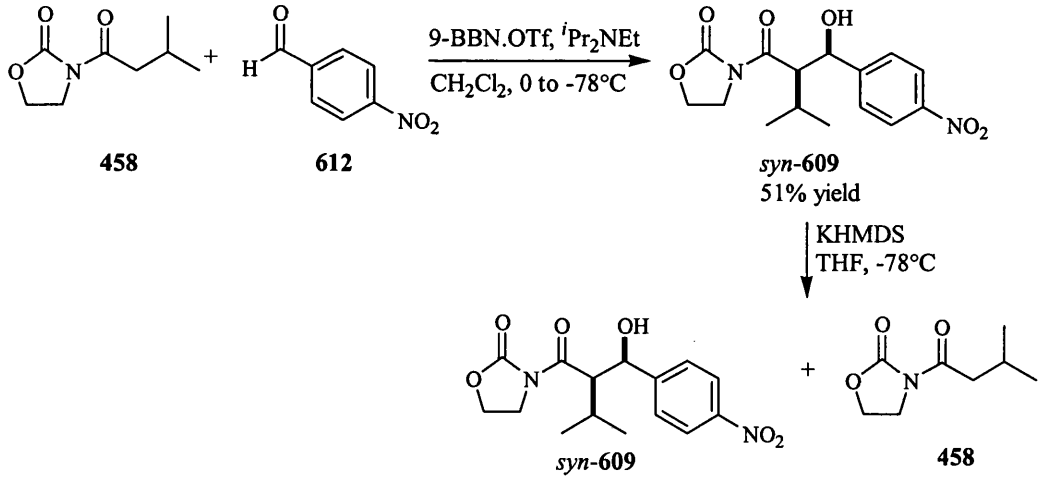


syn-**481**

(E)-**487**
69% yield
92% d.e.

Scheme 202

In order to determine if this lack of stereoselectivity during the rearrangement of *syn*-aldolates derived from aromatic aldehydes was a general trend, *syn*-aldolate **609** was next prepared *via* reaction of the boron enolate of *N*-acyl-oxazolidine-2-one **458** and *p*-nitrobenzaldehyde **612** in 70% yield (Scheme 203). This *syn*-aldolate **609** was then treated with 1.5 equivalents of KHMDS in THF at –78°C in the usual manner but failed to afford the desired amide, affording instead the starting material *syn*-**613**, along with product of the *retro*-aldol reaction *N*-acyl-oxazolidin-2-one **458** and unknown compounds.

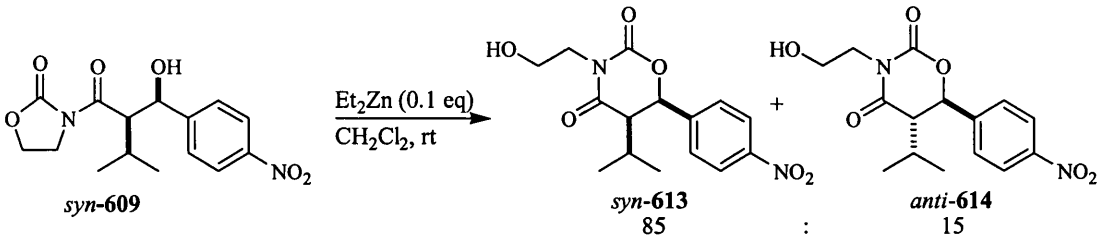


458 **612** *syn*-**609**
51% yield

syn-**609** **458**

Scheme 203

Treatment of *syn*-aldolate **609** with Et_2Zn at room temperature afforded a 85:15 mixture of oxazinane-2,4-diones *syn*-**613** and *anti*-**614**. Purification *via* column chromatography afforded *syn*-oxazinane-2,4-dione **613** in 51% yield and > 95% d.e. (Scheme 204).



Scheme 204

Clearly, these reactions demonstrated that the base-catalysed rearrangement of aldolates derived from aromatic aldehydes was not as stereoselective as the other *syn*-aldolates **476**, **479**, **480** and *anti*-**468** described in Chapter 5. In the light of the observation of a reversible *retro*-aldol/aldol pathway for the zinc alkoxide of chiral *syn*-aldolate **600**, it is proposed that equilibration of *syn*-oxazinane-2,4-diones to *anti*-oxazinane-2,4-diones (X = H) under these conditions is occurring *via* the *retro*-aldol mechanism described in Figure 56.

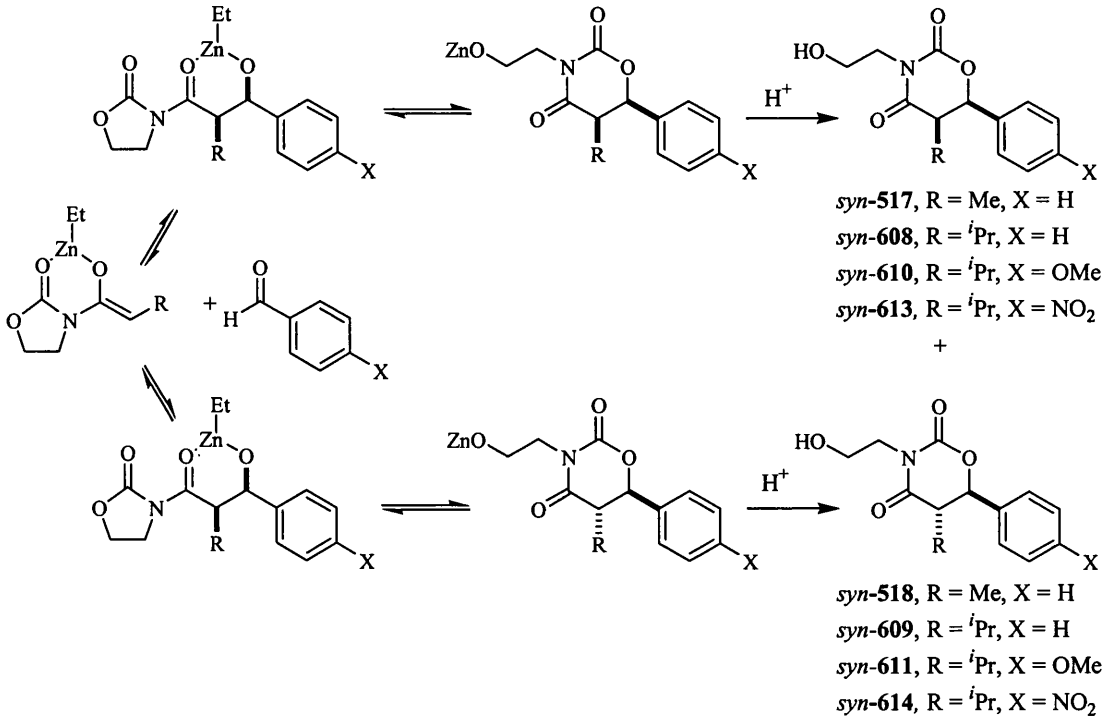
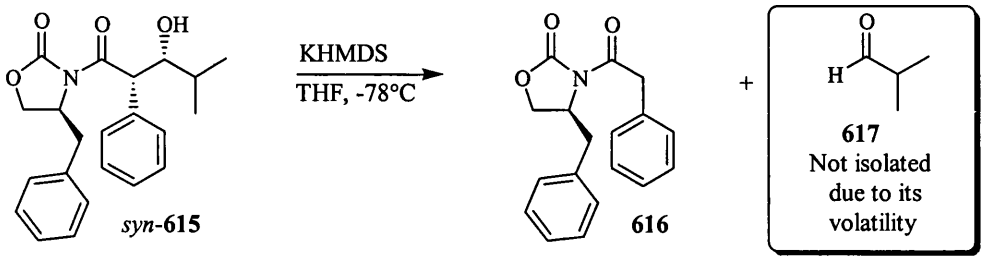


Figure 56

7.5 Conclusion and further developments

Given that the *retro*-aldol reaction of a chiral *syn*-aldolate derived from *N*-phenylacetyloxazolidin-2-one would afford an enolate stabilised by the presence of the α-aryl group, it was decided to next investigate the *retro*-aldol reaction of *syn*-aldolate **615**. Unfortunately, time considerations have prevented me from investigating this approach any further, however Matthew Cheeseman, another member of the SDB group, has found that treatment of *syn*-aldolate **615** with KHMDS in THF at -78°C, followed by dropwise

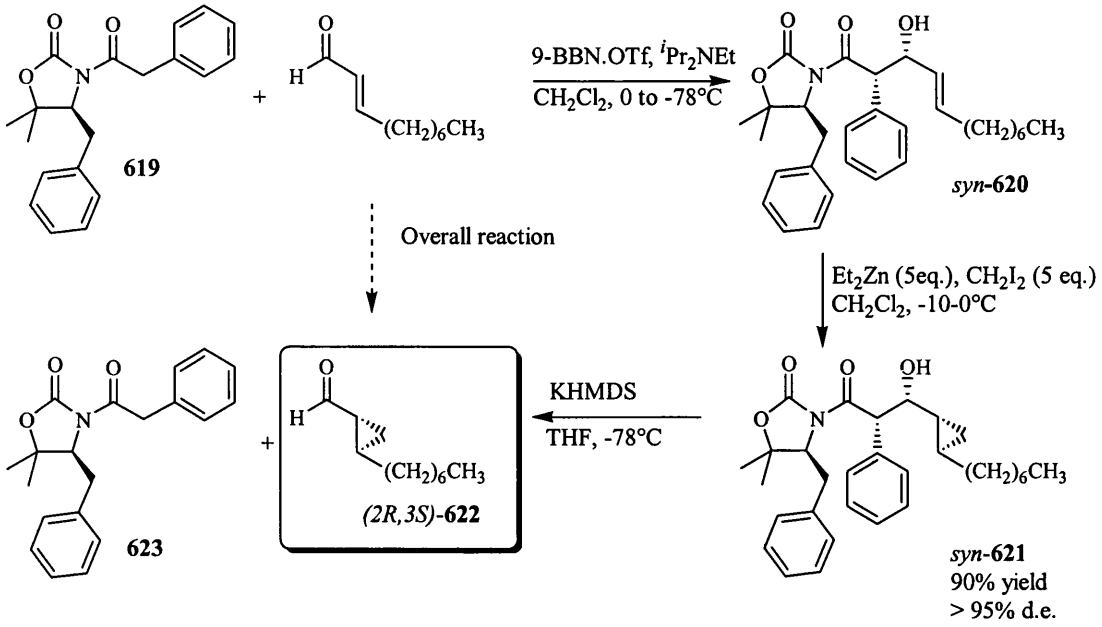
addition of saturated NH_4Cl_{aq} solution at -78°C, resulted in clean *retro*-aldol reaction to afford *N*-phenylacetyl-oxazolidin-2-one **616** and aldehyde **617** (not isolated) as the only products (Scheme 205). It is noteworthy that slow addition of NH_4Cl_{aq} was found to be crucial for avoiding decomposition of the enolate of *N*-phenylacetyl-oxazolidin-2-one **616** into its parent oxazolidin-2-one **471**.



Scheme 206

Thus, a suitable *N*-acyl-oxazolidine-2-one-*syn*-aldolate substrate has been identified that undergoes a clean *retro*-aldol reaction to occur on deprotonation with KHMDS at -78°C, a situation that would enable Step 3 of our original concept using chiral auxiliaries in a *novel* manner to be realised (see scheme 131).

The only step left to be realised in this protocol was therefore Step 2, which was to identify a suitable conditions that would enable a directed reaction to be carried out under the control of the β-hydroxyl-functionality of *syn*-aldolate with good stereocontrol. Building on the results described in this thesis, Matthew Cheeseman prepared *syn*-aldolate **620** using the 9-BBN.OTf boron enolate protocol in > 95% d.e. This *syn*-aldolate **620** was employed for a modified Simmons-Smith reaction, where the β-hydroxy group was used to direct the cyclopropanation of the allylic alcohol functionality to afford cyclopropane-*syn*-aldolate **621** in > 95% d.e. Subsequent purification of cyclopropane **621** to homogeneity *via* chromatography, followed by treatment with KHMDS in THF at -78°C and quenching at -78°C with NH_4Cl_{aq}, resulted in a clean *retro*-aldol reaction to afford *N*-phenylacetyl-oxazolidin-2-one **623**, and the diastereoisomerically pure aldehyde **622** in 85% yield (Scheme 206).



Scheme 6

Therefore, it is particularly gratifying that all of the hard-work that has been carried out in this thesis in optimising methodology for carrying out efficient aldol and *retro*-aldol reactions on *N*-acyl-oxazolidin-2-one-*syn*-aldolate substrates, has finally been successful in ultimately realising the original strategy for using chiral auxiliaries to prepare enantiopure aldehyde fragments in high d.e.

CHAPTER 8. Experimental

8-1 General conditions

Melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter. Infra red spectra were recorded in the range of 4000-600 cm^{-1} on a Perkin Elmer FT 1000 spectrometer with internal calibration. Absorption in the carbonyl region are presented in the following manner:

- carbon-hydrogen stretch in methoxy group, $(C\text{-}H)_{MeO}$
- carbonyl stretch in the oxazolidin-2-one, $(C{=}O)_{ox}$
- carbonyl stretch in the side chain, $(C{=}O)_{am}$
- carbon-carbon double bond stretch, (C=C)
- carbon-carbon double bond stretch in an aromatic ring, $(C{=}C)_{ar}$
- nitro group conjugated with a π system, $(N{=}O)_{conj}$

^1H NMR spectra were recorded on Bruker AM-300 spectrometers at 300 MHz. Chemical shifts (δ) are expressed in parts per million (ppm), and are relative to residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm), CH_3COCH_3 (δ_H = 2.12 ppm) or TMS (δ_H = 0 ppm). The multiplicities are presented in the following manner:

- singlet, s
- broad singlet, br s
- doublet, d
- doublet of doublets, dd
- doublet of doublets of doublets, ddd
- doublet of quartets of doublets, dqd
- apparent doublet of triplets, app dt
- doublet of septets, d of septets
- triplet, t
- apparent triplet, app t
- quartet, q
- quartet of doublets, qd
- apparent quartet, app q
- apparent pentet, app pentet
- septet of doublets, septet of d
- apparent octet, app octet
- apparent nonet, app nonet

Coupling constants (J) were measured in Hz. Diastereomeric excess were estimated from the relative intensities of the relevant peaks in the ^1H NMR. ^{13}C spectra were recorded in $CDCl_3$ or CD_3COCD_3, unless otherwise stated, at 75 MHz using the resonance of $CDCl_3$ (δ_C = 77 ppm, t) or CD_3COCD_3 (δ_C = 30.1 ppm, septet) as the internal reference.

Mass spectra were carried out either at the University of Bath (Finnigan MAT 8340 instrument) or at the University of Wales, Swansea (Finnigan MAT 900 XLT instrument) using techniques such as electron ionisation (EI, 70 eV), chemical ionisation (CI), fast atomic bombardment (FAB) and electrospray (ES). Ionisation gas for chemical ionisation will be specified between brackets for each analysis. Elemental analyses were performed using an Exeter Analytical Inc CE-440 Elemental analyser.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structural determination and refinement were achieved using the SHELZ suite of programmes; drawings were produced using ORTEX.

Analytical thin layer chromatography was performed on pre-coated aluminium-backed silica gel (Merck Kieslegel 60 F_{254}) plates or pre-coated aluminium-backed aluminium oxide gel (Merck Kieslegel 60 F_{254}). Plates were visualised under ultra-violet light (at 254 nm) or by staining with potassium permanganate or vanillin followed by heating. Column chromatography was carried out using Merck Kieselgel 60H silica gel or Acros Organics aluminium oxide gel, neutral, 50-200 μm. Samples were added on top of the column as pre-absorbed on silica or as concentrated solutions.

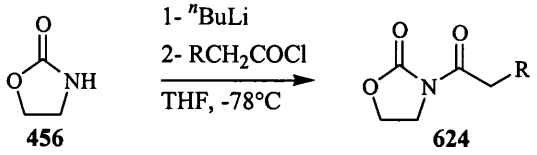
Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl, and dichloromethane from CaH_2 all under nitrogen. Petrol refers to light petroleum, bp 40-60 ^{o}C, ether refers to diethyl ether.

Unless otherwise stated, commercially available starting materials were used throughout without any further purification. Reactions requiring anhydrous conditions were performed under nitrogen or argon in oven or flame dried apparatus.

8.2 Preparation of acylated oxazolidin-2-ones

Procedures for the preparation of *N*-acyl oxazolidin-2-ones:

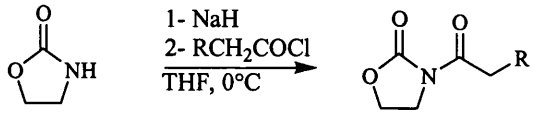
General protocol A[151]



456 **624**

A solution of *n*butyllithium in hexanes (1.1 eq.) was added dropwise *via* syringe to a stirred solution of oxazolidin-2-one **457** (1 eq.) in THF at -78°C under a nitrogen atmosphere and the mixture was allowed to stir for 15 minutes. Acyl chloride (1.1 eq.) was added at –78°C. The reaction was stirred at this temperature for 2 hours and allowed to warm to room temperature over a 1-hour period. Saturated NH_4Cl_{aq} was added and the reaction extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with $NaHCO_{3aq}$ and brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford *N*-acyl oxazolidin-2-one **460.**

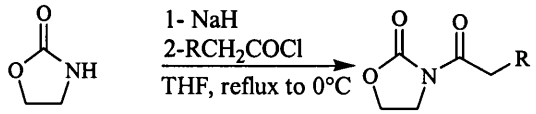
General protocol B[179]



456 **624**

A 60% dispersion of sodium hydride in mineral oil (1.5 eq.) was added to a stirred solution of oxazolidin-2-one **456** (1 eq.) in THF at 0°C under a nitrogen atmosphere and the mixture allowed to stir for 2 hours. Acyl chloride (1.55 eq.) was added at 0°C and the reaction was stirred for 3 hours at this temperature. Saturated NH_4Cl_{aq} was added and the reaction extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford *N*-acyl oxazolidin-2-one **624**.

General protocol C[177]

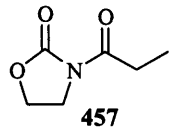


456 **624**

A 60% dispersion of sodium hydride in mineral oil (1.1 eq.) was added to a stirred solution of oxazolidin-2-one **456** (1 eq.) in THF at 0°C under a nitrogen atmosphere. The reaction was refluxed for one hour and then cooled to 0°C. Acyl chloride (1.05 eq.) was added at 0°C and the reaction stirred for 3 hours at this temperature. Saturated NH_4Cl_{aq} was added and the reaction extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed

with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford *N*-acyl oxazolidin-2-one **624**.

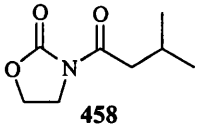
3-propionyl-1,3-oxazolidin-2-one 457[164]



457

Reaction of oxazolidin-2-one **456** (5.000 g, 57.47 mmol) with a 2.5M solution of ^{n}butyllithium in hexanes (25.30 mL, 63.2 mmol) and propionyl chloride (5.16 g, 63.2 mmol) in THF (250 mL), according to general protocol A, afforded after recrystallisation from hot ethyl acetate the title compound **457** (5.940 g, 41.54 mmol) in 72% yield as a white crystalline solid, *mp* 77-79°C (lit,[164] 80-81°C); ν_{max} *(KBr disc)/cm*$^{-1}$ 1773 $(C{=}O)_{ox}$, 1700 $(C{=}O)_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 1.17 (3H, t, *J* 7.5, CH_2CH_3), 2.94 (2H, q, *J* 7.5, CH_2CH_3), 4.02 (2H, app t, *J* 8.0, CH_2N), 4.42 (2H, app t, *J* 8.0, CH_2O); δ_C *(CDCl$_3$)* 8.7, 29.1, 42.9, 62.4, 154.0, 174.6; *m/z* ($EI^{+\cdot}$) 143 (49, $M^{+\cdot}$), 57 (100%, $CH_3CH_2CO^+$); (Found ($EI^{+\cdot}$) M^+ 143.0574 $C_6H_9NO_3$ requires 143.0577).

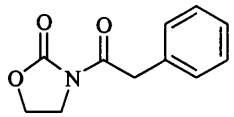
3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458[180]



458

Reaction of oxazolidin-2-one **456** (9.905 g, 113.85 mmol) with a 2.5M solution of ^{n}butyllithium in hexanes (50.10 mL, 125.23 mmol) and *iso*-valeryl chloride (21.50 mL, 125.23 mmol) in THF (500 mL), according to general protocol A, afforded after purification through silica gel chromatography (40% ethyl acetate/petrol) the title compound **458** (14.408 g, 84.26 mmol) in 74% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 1779 $(C{=}O)_{ox}$, 1699 $(C{=}O)_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 0.99 (6H, d, *J* 7.0, $CH(CH_3)_2$), 2.18 (1H, app nonet, *J* 7.0, $CH(CH_3)_2$), 2.81 (2H, d, *J* 7.0, $CH_2{}^i$Pr), 4.03 (2H, app t, *J* 8.0, CH_2N), 4.42 (2H, app t, *J* 8.0, CH_2O); δ_C *(CDCl$_3$)* 22.7, 22.8, 25.3, 42.9, 43.9, 62.3, 153.9, 173.2; *m/z* (CI^+, *iso*-butane) 172 (85, MH^+), 129 (82, MH^+-$CH(CH_3)_2$), 85 (100%); (Found (FAB^+) MH^+ 172.0974 $C_8H_{14}NO_3$ requires 172.0974).

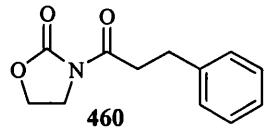
3-(2-phenylacetyl)-1,3-oxazolidin-2-one 459[177]



459

Reaction of oxazolidin-2-one **456** (9.900 g, 113.79 mmol) with a 1.6M solution of ^{n}butyllithium in hexanes (78.20 mL, 125.17 mmol) and phenyl acetyl chloride (21.50 mL, 125.17 mmol) in THF (500 mL), according to general protocol A, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound **459** (14.404 g, 70.26 mmol) in 62% yield as a white solid, *mp* 61-63°C (lit.,[177] 64-65°C); ν_{max} *(KBr disc)/cm*$^{-1}$ 3010 (C-H)$_{ar}$, 1773 (C=O)$_{ox}$, 1696 (C=O)$_{am}$, 1599 (C=C)$_{ar}$, 1507 (C=C)$_{ar}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 3.92 (2H, app t, *J* 8.0, C*H*$_2$N), 4.25 (2H, s, C*H*$_2$Ph), 4.29 (2H, app t, *J* 8.0, C*H*$_2$O), 7.26-7.31 (5H, m, Ph-*H*); δ_C *(CDCl$_3$)* 12.2, 13.8, 63.2, 128.1, 129.4, 130.0, 131.6, 154.7, 172.3; *m/z* (EI^{+}) 205 (30, M^{+}), 118 (100), 91 (60%, PhCH$_2^{+}$); (Found (EI^{+}) M^{+} 205.0742 $C_{11}H_{11}NO_3$ requires 205.0739).

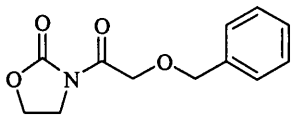
3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one 460



460

Reaction of oxazolidin-2-one **456** (1.496 g, 17.20 mmol) with a 2.5M solution of ^{n}butyllithium in hexanes (7.60 mL, 18.91 mmol) and phenylpropionyl chloride (2.80 mL, 18.91 mmol) in THF (90 mL), according to general protocol A, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound **460** (2.765 g, 12.63 mmol) in 73% yield as a white solid, *mp* 100-101°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3008 (C-H)$_{ar}$, 1765 (C=O)$_{ox}$, 1692 (C=O)$_{am}$, 1602 (C=C)$_{ar}$, 1484 (C=C)$_{ar}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 2.91 (2H, t, *J* 7.5, C*H*$_2$CH$_2$Ph), 3.17 (2H, t, *J* 7.5, CH$_2$C*H*$_2$Ph), 3.90 (2H, app t, *J* 8.0, C*H*$_2$N), 4.29 (2H, app t, *J* 8.0, C*H*$_2$O), 7.09-7.24 (5H, m, Ph-*H*); δ_C *(CDCl$_3$)* 30.6, 37.2, 42.9, 62.5, 126.6, 128.8, 128.9, 140.9, 153.9, 172.9; *m/z* (EI$^{+\cdot}$) 219 (55, $M^{+\cdot}$), 132 (27, PhCH$_2$CH$_2$CO^{+}), 104 (100), 88 (87, $M^{+\cdot}$-PhCH$_2$CH$_2$CO$^{\cdot}$); (Found (ES^{+}) MNH$_4^{+}$ 237.1237 $C_{12}H_{17}N_2O_3$ requires 237.1234).

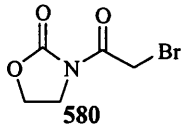
3-[2-(benzyloxy)acetyl]-1,3-oxazolidin-2-one 571



571

Reaction of oxazolidin-2-one **456** (0.500 g, 5.74 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.345 g, 8.61 mmol) and benzyloxyacetyl chloride (1.40 mL, 8.90 mmol) in THF (25 mL), according to general protocol B, afforded after recrystallisation from hot ethyl acetate the title compound **571** (1.071 g, 4.56 mmol) in 79% yield as a white solid, *mp* 128-130°C ; ν_{max} *(KBr disc)/cm*$^{-1}$ 1761 $(C{=}O)_{ox}$, 1718 $(C{=}O)_{am}$, 1607 $(C{=}C)_{ar}$, 1498 $(C{=}C)_{ar}$, 1144 (C-O); δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 3.96 (2H, app t, *J* 8.0, CH_2O), 4.39 (2H, app t, *J* 8.0, CH_2N), 4.60 (2H, s, CH_2OCH_2Ph), 4.62 (2H, s, CH_2OCH_2Ph), 7.23-7.34 (5H, m, Ph-*H*); δ_C *(CDCl$_3$)* 42.4, 63.5, 69.8, 73.8, 128.4, 128.5, 128.9, 137.5, 153.9, 170.6; *m/z* ($EI^{+\cdot}$) 253 (100, MNH_4^+), 236 (60%, $MH^{+\cdot}$); (Found (ES^+) MH^+ 236.0918 $C_{12}H_{14}NO_4$ requires 236.0917).

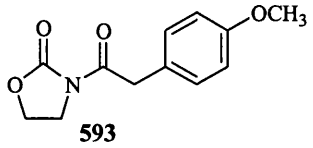
3-(2-bromoacetyl)-1,3-oxazolidin-2-one 580[173]



580

Reaction of oxazolidin-2-one **456** (1.500 g, 17.24 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.792 g, 19.85 mmol) and bromoacetyl bromide (1.60 mL, 18.10 mmol) in THF (90 mL), according to general protocol C, afforded after purification through silica gel chromatography (40% ethyl acetate/petrol) the title compound **580** (2.61 g, 12.63 mmol) in 73% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 1777 $(C{=}O)_{ox}$, 1712 $(C{=}O)_{am}$, 758 (C-Br); δ_H *(300MHz, CDCl$_3$)* 4.07 (2H, app t, *J* 8.5, CH_2N), 4.48 (2H, app t, *J* 8.5, CH_2O), 4.50 (2H, s, CH_2Br); δ_C *(CDCl$_3$)* 28.1, 43.1, 63.0, 153.5, 166.5; *m/z* ($EI^{+\cdot}$) 207-209 (7, $M^{+\cdot}$), 128 (100%, $M^{+\cdot}$-Br$^{\cdot}$); (Found (ES^+) MNH_4^+ 224.9871 $C_5H_{10}N_2O_3Br$ requires 224.9869).

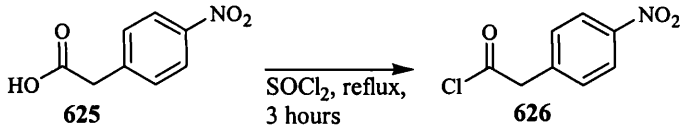
3-[2-(4-methoxyphenyl)acetyl]-1,3-oxazolidin-2-one 593



593

Reaction of oxazolidin-2-one **456** (0.500 g, 5.74 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.344 g, 8.61 mmol) and *p*-methoxyphenylacetyl chloride (1.40 mL, 8.90 mmol) in THF (30 mL), according to general protocol B, afforded after purification through silica gel chromatography (gradient, 15-30% ethyl acetate/petrol) the title compound **593** (1.112 g, 4.72 mmol) in 69% yield as a white solid, *mp* 114-115°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3017 (C-H)$_{ar}$, 2832 (C-H)$_{MeO}$, 1769 (C=O)$_{ox}$, 1709 (C=O)$_{am}$, 1614 (C=C)$_{ar}$, 1585 (C=C)$_{ar}$, 1519 (C=C)$_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 3.72 (3H, s, ArOCH_3), 3.94 (2H, app t, *J* 8.0, CH_2O), 4.14 (2H, s, CH_2Ar), 4.32 (2H, app t, *J* 8.0, CH_2N), 6.79 (2H, d, *J* 9.0, Ar-*H*), 7.16 (2H, d, *J* 9.0, Ar-*H*); δ_C *($CDCl_3$)* 40.6, 43.1, 55.6, 62.4, 114.3, 125.9, 131.2, 153.9, 159.1, 172.0; *m/z* (EI$^{+\cdot}$) 235 (23, $M^{+\cdot}$), 148 (100%, $ArCH_2CO^+$); (Found (ES$^+$) MNH_4^+ 253.1186 $C_{12}H_{17}N_2O_4$ requires 253.1183); (Found: C, 60.9; H, 5.43; N, 5.84 $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.57; N, 5.95%).

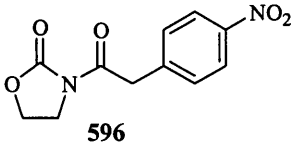
***p*-nitrophenylacetyl chloride 626**



625 **626**

A solution of *p*-nitrophenyl acetic acid **625** (3.327 g, 18.33 mmol) was refluxed for 3 hours in thionyl chloride (20 mL). Evaporation of the solvent afforded the title compound **626** (2.912 g, 14.61 mmol) in 80% yield as a yellow solid, δ_H *(300MHz, $CDCl_3$, Me_4Si)* 4.21 (2H, s, CH_2Ar), 7.40 (2H, d, *J* 9.0, Ar-*H*), 8.18 (2H, d, *J* 9.0, Ar-*H*); δ_C *($CDCl_3$)* 52.7, 124.5, 131.0, 138.6, 148.2, 171.2.

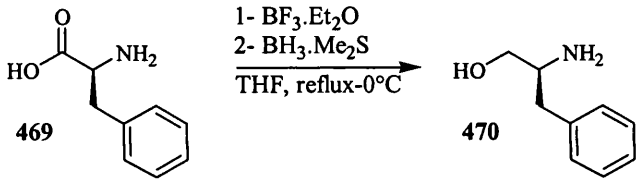
3-[2-(4-nitrophenyl)acetyl]-1,3-oxazolidin-2-one 596



596

Reaction of oxazolidin-2-one **456** (0.500 g, 5.74 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.330 g, 8.21 mmol) and *p*-nitrophenylacetyl chloride **626** (1.702 g, 8.52 mmol) in THF (25 mL), according to general protocol B, afforded after separation through silica gel chromatography (gradient: 20-30% ethyl acetate/petrol) the title compound **626** (0.343 g, 1.37 mmol) in 24% yield as a yellow solid, *mp* 154-156°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3111 $(C\text{-}H)_{ar}$, 1776 $(C{=}O)_{ox}$, 1695 $(C{=}O)_{am}$, 1606 $(C{=}C)_{ar}$, 1516 $(N{=}O)_{conj}$, 1348 $(N{=}O)_{conj}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 3.99 (2H, app t, *J* 8.0, CH_2N), 4.32 (2H, s, CH_2Ar), 4.39 (2H, app t, *J* 8.0, CH_2O), 7.41 (2H, d, *J* 9.0, Ar-*H*), 8.11 (2H, d, *J* 9.0, Ar-*H*); δ_C *($CDCl_3$)* 41.4, 43.0, 62.6, 124.2, 131.2, 141.3, 147.6, 153.9, 170.2; *m/z* (CI^+, *iso*-butane) 251 (29, MH^+), 182 (100%); (Found (ES^+) MH^+ 251.0657 $C_{11}H_{11}N_2O_5$ requires 251.0662).

***(2S)*-2-amino-3-phenyl-1-propanol 470**[181]

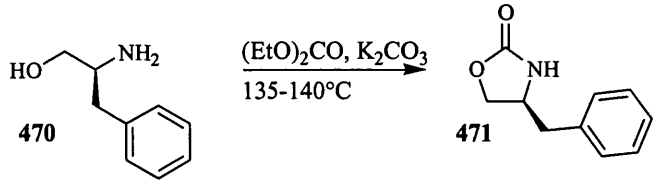


469 **470**

Boron trifluoride-etherate (15.30 mL, 121.20 mmol) was added dropwise to a solution of (*S*)-phenylalanine **469** (20.000 g, 121.01 mmol) in THF (60 mL) in a flame-dried, 250-mL, 3-necked, round-bottomed flask equipped with a pressure equalising addition funnel and an 18-inch Vigreux column with a distillation head. The reaction was refluxed for 1 hour, after which the solid material had completely dissolved. Reaction temperature was adjusted to just below the reflux point, and $BH_3.Me_2S$ (12.70 mL, 133.30 mmol) was added dropwise over 20 min. During the addition, hydrogen evolved, and methyl sulphide was allowed to distil as it was liberated. The reaction was then refluxed for 6 hours and cooled to room temperature. A 1:1 mixture of THF/water (15 mL) followed with 5M $NaOH_{aq}$ (90 mL) was added carefully and reaction mixture was refluxed for additional 12 hours. The remaining THF was removed *in vacuo*, and the resulting slurry extracted with CH_2Cl_2 (5 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound **470**. Recrystallisation from hot ethyl acetate afforded *(2S)*-2-amino-3-phenyl-1-propanol **470** (13.600 g, 90.10

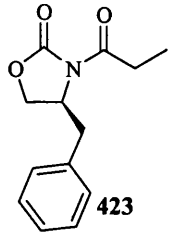
mmol) in 74% yield as white needles, $[\alpha]_D^{25}$ -23.5 (c 1.03, ethanol) [lit,[181] -22.4 (c 1.03, ethanol)]; *mp* 89-91°C (lit,[181] 88.5-91°C); ν_{max} *(KBr disc)/cm*$^{-1}$ 3393 (br, OH, NH), 1602 $(C{=}C)_{ar}$, 1494 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.80 (3H, br s, O*H*, NH_2), 2.52 (1H, dd, *J* 13.5, 8.5, CH_AH$_B$Ph), 2.80 (1H, dd, *J* 13.5, 5.0, CH$_A$$H_B$Ph), 3.08-3.17 (1H, m, C*H*NH_2), 3.38 (1H, dd, *J* 10.5, 7.5, CH_AH$_B$OH), 3.64 (1H, dd, *J* 10.5, 4.0, CH$_A$$H_B$OH), 7.18-7.34 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 41.2, 54.6, 66.3, 126.9, 129.0, 129.6, 138.8.

(4*S*)-4-benzyl-1,3-oxazolidin-2-one 471[181]



Potassium carbonate (1.250 g, 9.01 mmol), and diethyl carbonate (21.300 g, 180.10 mmol) were added to (*S*)-phenylalaninol **456** (13.602 g, 90.10 mmol) in a dry, 100mL, 3-necked, round-bottomed flask equipped with a thermometer, an 18-inch Vigreux column with a distillation head. The reaction was heated to 135-140°C, and ethanol was allowed to distil as it was formed for 2 hours. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered to remove most of the remaining potassium carbonate. The reaction was washed with $NaHCO_{3aq}$ and brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford the title compound **471.** Recrystallisation from a mixture of ethyl acetate and petrol afforded (4*S*)-4-benzyl-1,3-oxazolidin-2-one **471** (13.305 g, 75.1 mmol) in 83% yield as a white crystalline solid, $[\alpha]_D^{25}$ +5.5 (c 1.09, ethanol) [lit,[181] +4.9 (c 1.10, ethanol)]; *mp* 84-86°C (lit,[181] 84.5-86.5°C); ν_{max} *(KBr disc)/cm*$^{-1}$ 3281 (s, NH), 1748 $(C{=}O)_{ox}$, 1711 $(C{=}O)_{amII}$, 1602 $(C{=}C)_{ar}$, 1496 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 2.84 (1H, dd, *J* 13.5, 7.0, CH_AH$_B$Ph), 2.91 (1H, dd, *J* 13.5, 7.0, CH$_A$$H_B$Ph), 4.04-4.17 (2H, m, C$H_AH_B$O, C*H*NH), 4.42 (1H, app t, *J* 8.0, CH$_A$$H_B$O), 6.12 (1H, br s, N*H*), 7.15-7.37 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 41.8, 54.2, 70.0, 127.6, 129.4, 129.4, 136.3, 160.0; (Found: C, 67.5; H, 6.26; 7.88. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.26; N, 7.90%).

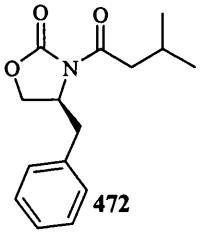
(4S)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one 423[151]



423

Reaction of *(S)*-4-benzyl-oxazolidin-2-one **471** (5.001 g, 28.25 mmol) with a 2.5M solution of ^{n}butyllithium in hexanes (12.40 mL, 31.08 mmol) and propionyl chloride (2.70 mL, 31.08 mmol) in THF (120 mL), according to general protocol A, afforded after recrystallisation from hot ethyl acetate the title compound **423** as a white crystalline solid (6.322 g, 27.13 mmol) in 96% yield, $[\alpha]_D^{25}$ +100.0 (c 1.02, ethanol) [lit,[151] +99.5, (c 1.01, ethanol)]; *mp* 43-45°Ç (lit,[181] 44-46°C); ν_{max} *(KBr disc)/cm*$^{-1}$ 1786 $(C{=}O)_{ox}$, 1701 $(C{=}O)_{am}$, 1602 $(C{=}C)_{ar}$, 1496 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.13 (3H, t, *J* 7.5, CH_3), 2.70 (1H, dd, *J* 13.5, 9.5, CH_AH_BPh), 2.78-2.99 (2H, m, CH_2CH_3), 3.23 (1H, dd, *J* 13.5, 3.0, CH_AH_BPh), 4.07-4.16 (2H, m, CH_2O), 4.56-4.64 (1H, m, CHN), 7.13-7.30 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 8.7, 29.6, 38.3, 55.6, 66.6, 127.7, 129.3, 129.8, 135.7, 153.9, 174.5; *m/z* (CI^+, NH_3) 251.2 (100, MNH_4^+), 234 (55, MH^+), 91 (51%, $PhCH_2$).

(4S)-4-benzyl-3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 472



472

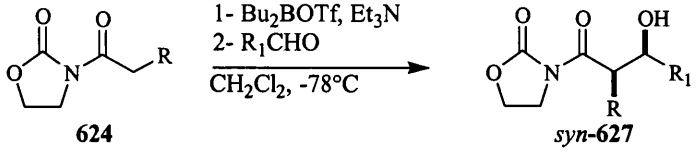
Reaction of *(S)*-4-benzyl-oxazolidin-2-one **471** (3.995 g, 22.57 mmol) with a 1.6M solution of ^{n}butyllithium in hexanes (15.50 mL, 24.83 mmol) and *iso*-valeryl chloride (4.30 mL, 24.83 mmol) in THF (120 mL), according to general protocol A, afforded after purification through silica gel chromatography (30% ethyl acetate/petrol) the title compound **472** (3.392 g, 13.00 mmol) in 57% yield as a white crystalline solid, $[\alpha]_D^{25}$ +61.5 (c 1.04, $CHCl_3$); *mp* 50-51°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3032 $(C\text{-}H)_{ar}$, 1787 $(C{=}O)_{ox}$, 1694 $(C{=}O)_{am}$, 1604 $(C{=}C)_{ar}$, 1491 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$)* 1.01 (3H, d, *J* 6.5, CH_3), 1.03 (3H, d, *J* 6.5, CH_3), 2.22 (1H, app nonet, *J* 6.5, $CH(CH_3)_2$), 2.75 (1H, dd, *J* 13.0, 9.5, CH_AH_BPh), 2.78 (1H, dd, *J* 16.0, 6.5, $CH_AH_BCH(CH_3)_2$), 2.90 (1H, dd, *J* 16.0, 6.5, $CH_AH_BCH(CH_3)_2$), 3.31 (1H, dd, *J* 13.0, 3.0, CH_AH_BPh), 4.17 (2H, m, CH_2O), 4.68 (1H,

m, C*H*N), 7.15-7.40 (5H, m, Ph-*H*); δ_C *(CDCl₃)* 22.8, 22.9, 25.4, 38.4, 44.4, 55.5, 66.5, 127.7, 129.3, 129.8, 135.7, 153.8, 173.1; *m/z* (CI^+, NH_3) 279 (100, MNH_4^+), 262 (62%, MH^+); (Found: C, 68.9; H, 7.31; N, 5.42. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.33; N, 5.36%).

8.3 Preparation of aldol products

Procedures to prepare *syn*-aldolate products:

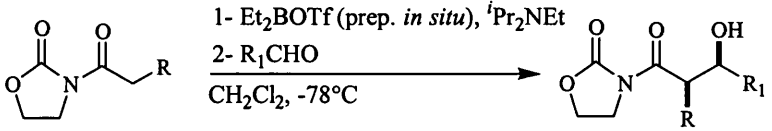
General protocol D[151]



624 ***syn*-627**

Triethylamine (1.6 eq.) was added *via* syringe to a stirred solution of *N*-acyloxazolidin-2-one **624** (1 eq.) in CH_2Cl_2 at –78°C under a nitrogen atmosphere and the mixture allowed to stir for 5 minutes. A 1.0M solution of Bu_2BOTf in CH_2Cl_2 (1.5 eq.) was added at –78°C. The reaction was stirred for 1 hour at this temperature and allowed to warm to 0°C for 20 minutes. The reaction was cooled down to –78°C, aldehyde (1.1 eq.) was added in one portion and the mixture allowed to stir for 30 minutes at –78°C. The reaction was allowed to warm to 0°C for 30 minutes. A 1M solution of NaOAc in 90% methanol/water (5 mL) was added and after 5 min, 30% aqueous H_2O_2 (0.5 mL) was added dropwise (caution: initial reaction is exothermic). The reaction was extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with $NaHCO_{3aq}$ and brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the *syn*-aldolate **627**.

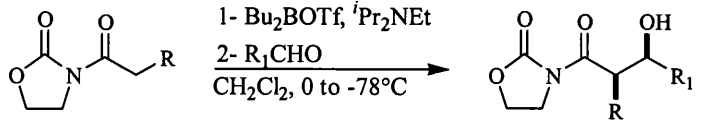
General protocol E



624 ***syn*-627**

Trifluoromethanesulfonic acid (1.2 eq.) was added to a 1.0M solution of Et_3B in hexanes (1.2 eq.) at room temperature. Reaction mixture was heated up to 40°C, stirred for 10 minutes and cooled down to 0°C. A solution of *N*-acyloxazolidin-2-one **624** (1 eq.) in CH_2Cl_2 was added and allowed to stir for 10 minutes. *N,N*-diisopropylethylamine (1.4 eq.) was added and the reaction was stirred for 20 minutes at 0°C and cooled down to –78°C. Aldehyde (1.1 eq.) was added, stirred during 30 min and the mixture warmed to 0°C over 1 hour. pH 7.0 phosphate buffer was added, allowed to stir for 5 min and a 2:1 solution of methanol/hydrogen peroxide added dropwise. Reaction was extracted with CH_2Cl_2 (x 3), the combined organic extracts were washed with $NaHCO_{3aq}$, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the *syn*-aldolate **627**.

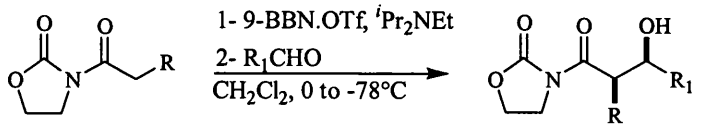
General protocol F



624 *syn*-**627**

A 1.0M solution of Bu_2BOTf in CH_2Cl_2 (1.2 eq.) was added *via* syringe to a stirred solution of *N*-acyloxazolidin-2-one **624** (1 eq.) in CH_2Cl_2 at 0°C and allowed to stir at this temperature for 5 minutes. *N,N*-diisopropylethylamine (1.4 eq.) was added, the reaction stirred for 25 minutes at 0°C and cooled down to –78°C. Aldehyde (1.1 eq.) was added, and the reaction was stirred for 2 hours and allowed to warm to 0°C for 30 minutes. pH 7.0 phosphate buffer was added, allowed to stir for 5 min and a 2:1 solution of methanol/hydrogen peroxide added dropwise. The reaction was extracted with CH_2Cl_2 (x 3) and the combined organic extracts were washed with $NaHCO_{3aq}$, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the *syn*-aldolate **627**.

General protocol G

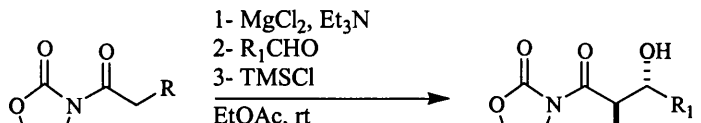


624 *syn*-**627**

Same procedure as in General protocol F, a 0.5M solution of 9-BBN.OTf in hexanes was used as the Lewis acid.

Procedures for the preparation of *anti*-aldolates:

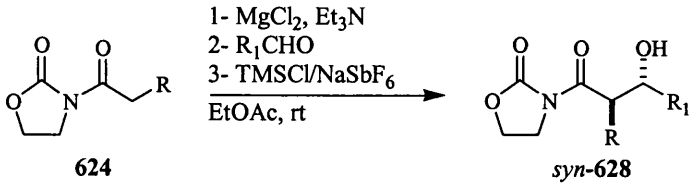
General protocol H[154]



624 *anti*-**628**

Magnesium chloride (0.1 eq.), triethylamine (2 eq.), aldehyde (1.2 eq.) and chlorotrimethylsilane (1.5 eq.) were added successively to a solution of *N*-acyloxazolidin-2-one **624** (1 eq.) in THF at room temperature. Reaction was stirred for 24 hours and pushed through a plug of silica (5 cm x 1 cm) with Et_2O (50 mL). The ether solution was concentrated *in vacuo*, methanol added along with 2 drops of trifluoroacetic acid and the reaction stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure to afford *anti*-aldolate **628**.

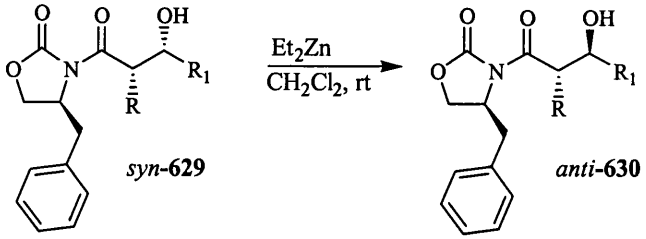
General protocol I[154]



624 ***syn*-628**

Same procedure as in General protocol H, sodium hexafluoroantimonate (0.3 eq.) was used to accelerate the reaction.

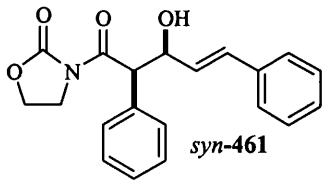
General protocol J



***syn*-629** ***anti*-630**

A 1.0M solution of Et_2Zn in toluene (0.1 eq.) was added dropwise to a stirred solution of *syn*-aldolate **629** (1 eq.) in CH_2Cl_2 at room temperature. The reaction was stirred for 2 hours. Saturated NH_4Cl_{aq} was added and the reaction extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford *anti*-aldolate **630**.

***syn*-3-[(*E*)-3-Hydroxy-2,5-diphenyl-4-pentenoyl]-1,3-oxazolidin-2-one 461**

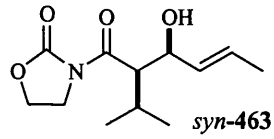


***syn*-461**

Reaction of 3-(2-phenylacetyl)-1,3-oxazolidin-2-one **459** (0.200 g, 0.98 mmol) with a 1.0M solution of Bu_2BOTf in CH_2Cl_2 (1.45 mL, 1.45 mmol), triethylamine (0.22 mL, 1.58 mmol) and *trans*-cinnamaldehyde (0.47 mL, 6.44 mmol) in CH_2Cl_2 (5 mL), according to general protocol D, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound *syn*-**461** (0.125 g, 0.37 mmol) in 38% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3532 (br, OH), 1778 $(C{=}O)_{ox}$, 1694 $(C{=}O)_{am}$, 1599 $(C{=}C)_{ar}$, 1494 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 2.45 (1H, br s, O*H*), 3.89 (1H, ddd, *J* 11.0, 9.0, 7.0, CH_AH_BN), 3.99 (1H, ddd, *J* 11.0, 9.0, 7.0, CH_AH_BN), 4.24 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.29 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.95 (1H, app t, *J* 7.0, C*H*OH), 5.24

(1H, d, *J* 7.0 C*H*Ph), 6.20 (1H, dd, *J* 16.0, 7.0, C*H*=CHPh), 6.65 (1H, d, *J* 16.0, CH=C*H*Ph), 7.21-7.50 (10H, m, Ph-*H*); δ_C *(CDCl₃)* 42.6, 54.9, 61.7, 74.0, 126.6, 127.8, 128.1, 128.4, 128.5, 128.7, 129.9, 132.5, 133.9, 136.5, 152.8, 172.7; *m/z* (CI^+, NH_3) 355 (41, MNH_4^+), 338 (12, MH^+), 337 (50, M^+), 320 (100%, M^+-OH); (Found (ES^+) MNH_4^+ 355.1653 $C_{20}H_{23}N_2O_4$ requires 355.1652).

syn-3-[(*E*)-3-Hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one 463



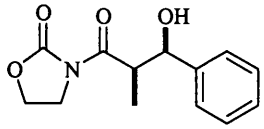
syn-**463**

General protocol D. Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (0.164 g, 0.96 mmol) with Bu_2BOTf (1.15 mL, 1.15 mmol), triethylamine (0.18 mL, 1.25 mmol) and *trans*-crotonaldehyde (0.09 mL, 1.06 mmol) in CH_2Cl_2 (5 mL) afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound *syn*-**463** (0.097 mg, 0.40 mmol) in 42% yield as a white solid.

General protocol E. Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (0.164 g, 0.96 mmol) with a 1.0M solution of Et_3B in hexanes (1.91 mL, 1.91 mmol), trifluoromethane sulfonic acid (0.17 mL, 1.91 mmol), *N,N*-diisopropylethylamine (0.39 mL, 2.23 mmol) and *trans*-crotonaldehyde (0.15 mL, 1.75 mmol) in CH_2Cl_2 (5 mL) afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound *syn*-**463** (0.229 g, 0.95 mmol) in 60% yield as a white solid.

General protocol G. Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (0.965 g, 5.85 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (14.10 mL, 7.02 mmol), *N,N*-diisopropylethylamine (1.32 mL, 7.60 mmol) and *trans*-crotonaldehyde (0.53 mL, 6.44 mmol) in CH_2Cl_2 (30 mL) afforded after purification through silica gel chromatography (25 % ethyl acetate/petrol) the title compound *syn*-**463** (1.090 g, 4.54 mmol) in 72% yield as a low-melting point white solid, ν_{max} *(nujol)/cm⁻¹* 3454 (br, OH), 1770 $(C=O)_{ox}$, 1690 $(C=O)_{am}$; δ_H *(300MHz, CDCl₃, Me₄Si)* 0.92 (3H, d, *J* 6.5, $CH(CH_3)_2$), 0.97 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.72 (3H, d, *J* 5.5, $CH=CHCH_3$), 1.99-2.11 (1H, m, $CH(CH_3)_2$), 2.23 (1H, br s, O*H*), 4.01-4.10 (3H, m, CH_2N, CH^iPr), 4.34-4.48 (3H, m, CH_2O, CHOH), 5.60-5.81 (2H, m, $CH=CHCH_3$); δ_C *(CDCl₃)* 18.2, 20.4, 21.1, 28.6, 43.2, 54.3, 62.0, 73.5, 130.0, 130.0, 154.7, 174.7; *m/z* (CI^+, *iso*-butane) 242 (6, MH^+), 224.1 (75, M^+-OH), 171.0 (64, M^+-$CHOHCHCHCH_3$), 156.0 (100%); (Found (FAB^+) MH^+ 242.1393 $C_{12}H_{20}NO_4$ requires 242.1392).

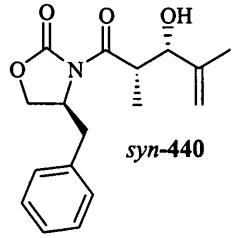
syn-3-(3-Hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 467[153]



syn-**467**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.545 g, 3.81 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (9.14 mL, 4.57 mmol), *N,N*-diisopropylethylamine (0.86 mL, 4.95 mmol) and benzaldehyde (0.43 mL, 4.19 mmol) in CH_2Cl_2 (20 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound *syn*-**467** (0.653 g, 2.62 mmol) in 69% yield as a white crystalline solid, *mp* 102-104°C (lit,[153] 105-106°C); ν_{max} *(KBr disc)/cm*$^{-1}$ 3561 (s, OH), 1766 $(C{=}O)_{ox}$, 1682 $(C{=}O)_{am}$, 1603 $(C{=}C)_{ar}$, 1494 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.15 (3H, d, *J* 7.0, CH_3), 3.07 (1H, d, *J* 3.0, O*H*), 3.95-4.07 (2H, m, CH_2N), 4.12 (1H, qd, *J* 7.0, 3.5, $CHCH_3$), 4.31-4.45 (2H, m, CH_2O), 5.13 (1H, app t, *J* 3.0, C*H*OH), 7.24-7.43 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 10.8, 43.0, 44.6, 62.4, 73.9, 126.4, 127.9, 128.6, 141.6, 153.5, 177.2; *m/z* (CI^+, NH_3) 267 (41, MNH_4^+), 250 (10, MH^+), 232 (38, M^+-OH), 206 (22, MH^+-CO_2), 161 (100%); (Found (ES^+) MH^+ 250.1081 $C_{13}H_{16}NO_4$ requires 250.1079).

***(4S)*-4-Benzyl-3-[*(2S,3S)*-3-hydroxy-2,4-dimethyl-4-pentenoyl]-1,3-oxazolidin-2-one 440**

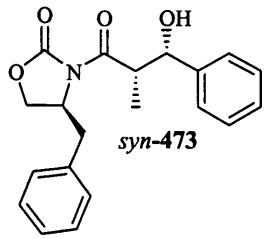


syn-**440**

Reaction of *(4S)*-4-benzyl-3-propionyl-1,3-oxazolidin-2-one **423** (0.998 g, 4.29 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (11.1 mL, 5.58 mmol), *N,N*-diisopropylethylamine (1.05 mL, 6.01 mmol) and methacrolein (0.40 mL, 4.72 mmol) in CH_2Cl_2 (20 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 10-20% ethyl acetate/petrol) the title compound *syn*-**440** (0.892 g, 2.94 mmol) in 69% yield as a colourless oil, $[\alpha]_D^{25}$ +59 (c 1.00, CH_2Cl_2); ν_{max} *(KBr disc)/cm*$^{-1}$ 3452 (s, OH), 1787 $(C{=}O)_{ox}$, 1695 $(C{=}O)_{am}$, 1653 (C=C), 1602 $(C{=}C)_{ar}$, 1498 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.19 (3H, d, *J* 7.0, $CHCH_3$), 1.74 (3H,

s, CH_2=C(CH_3)), 2.80 (1H, dd, *J* 13.0, 9.5, CH_AH_BPh), 2.94 (1H, d, *J* 3.0, OH), 3.28 (1H, dd, *J* 13.0, 3.5, CH_AH_BPh), 3.97 (1H, qd, *J* 7.0, 3.0, $CHCH_3$), 4.18-4.27 (2H, m, CH_2O), 4.37-4.44 (1H, m, CHN), 4.99 (1H, br s, CH_AH_B=C(CH_3)), 5.13 (1H, br s, CH_AH_B=C(CH_3)); δ_C *(CDCl3)* 10.4, 19.8, 38.1, 40.5, 55.6, 66.6, 74.3, 112.2, 127.8, 129.4, 129.8, 135.4, 144.0, 153.4, 177.5; *m/z* (CI^+, NH_3) 321 (28, MNH_4^+), 304 (57, MH^+), 286 (13, MH^+-H_2O), 251.1 (100), 234 (36%, MH^+-CHOHC(CH_3)=CH_2); (Found (ES^+) MH^+ 304.1549 $C_{17}H_{22}NO_4$ requires 304.1549).

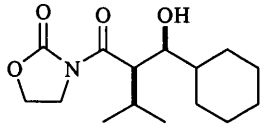
(4S)-4-Benzyl-3-{(2S)-2-[(S)-hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 473[151]



syn-**473**

Reaction of *(4R)*-4-benzyl-3-propionyl-1,3-oxazolidin-2-one **423** (0.700 g, 3.00 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (7.21 mL, 3.61 mmol), *N,N*-diisopropylethylamine (0.73 mL, 4.21 mmol) and benzaldehyde (0.34 mL, 3.30 mmol) in CH_2Cl_2 (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 10-20% ethyl acetate/petrol) the title compound *syn*-**473** (0.837 g, 2.47 mmol) in 82% yield as a colourless oil, $[\alpha]_D^{25}$ +69.8 (c 1.01, CH_2Cl_2) (lit,[151] +75.7, CH_2Cl_2, c 1.00); ν_{max} *(neat)/cm*$^{-1}$ 3488 (br, OH), 1773 $(C=O)_{ox}$, 1700 $(C=O)_{am}$; δ_H *(300MHz, CDCl3, Me4Si)* 1.15 (3H, d, *J* 7.0, CH_3), 2.70 (1H, dd, *J* 13.5, 9.5, CH_AH_BPh), 3.05 (1H, d, *J* 2.0, OH), 3.17 (dd, 1H, *J* 13.5, 3.3, CH_AH_BPh), 3.96-4.09 (3H, m, CH_2O, $CH(CH_3)$), 4.48-4.55 (1H, m, CHN), 5.02 (1H, d, *J* 2.6, CHOH), 7.11-7.34 (10H, m, Ph-H); δ_C *(CDCl3)* 11.3, 38.2, 44.9, 55.6, 66.6, 74.2, 126.5, 127.8, 128.0, 128.7, 129.4, 129.8, 135.4, 141.7, 153.3, 177.1; *m/z* ($EI^{+\cdot}$) 339 (6, $M^{+\cdot}$), 233 (63, $M^{+\cdot}$-PhCHOH$^{\cdot}$), 57 (100%); (Found (ES^+) MH^+ 340.1545 $C_{20}H_{22}NO_4$ requires 340.1543).

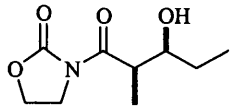
syn-3-{2-[Cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 476



syn-**476**

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (1.500 g, 8.77 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (21.11 mL, 10.53 mmol), *N,N*-diisopropylethylamine (1.99 mL, 11.40 mmol) and cyclocarboxaldehyde (1.17 mL, 9.65 mmol) in CH_2Cl_2 (40 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 10-20% ethyl acetate/petrol) the title compound **476** (1.451 g, 5.11 mmol) in 58% yield as a white solid, *mp* 131-133°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3510 (s, OH), 1773 $(C=O)_{ox}$, 1676 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.02 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.03 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.12-1.27 (4H, m, Cy-*H*), 1.30-1.38 (1H, m, Cy-*H*), 1.61-1.67 (2H, m, Cy-*H*), 1.73-1.77 (2H, m, Cy-*H*), 1.83-1.91 (1H, m, Cy-*H*), 2.04-2.10 (1H, m, Cy-*H*), 2.31 (1H, septet of d, *J* 7.0, 5.0, $CH(CH_3)_2$), 3.72-3.78 (1H, m, C*H*OH), 4.04 (2H, app t, *J* 8.0, CH_2N), 4.22 (1H, dd, *J* 7.0, 5.0, CH^iPr), 4.41 (2H, app dt, *J* 8.0, 1.8, CH_2O); δ_C *($CDCl_3$)* 19.6, 21.5, 26.6, 26.7, 26.8, 27.4, 28.2, 30.6, 41.7, 43.0, 49.3, 61.9, 76.0, 153.7, 175.6; *m/z* (FAB^+) 284 (97, MH^+), 266 (100%, M^+-OH); (Found (FAB^+) MH^+ 284.1868 $C_{15}H_{26}NO_4$ requires 284.1862).

syn-3-(3-Hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one 479

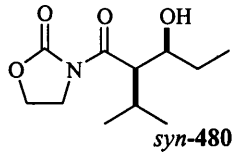


syn-**479**

Reaction of the 3-propionyl-1,3-oxazolidin-2-one **457** (0.991 g, 6.93 mmol) with a 1.0M solution of Bu_2BOTf in CH_2Cl_2 (8.39 mL, 8.39 mmol), *N,N*-diisopropylethylamine (1.70 mL, 9.79 mmol) and propionaldehyde (0.56 mL, 7.69 mmol) in CH_2Cl_2 (35 mL), according to general protocol F, afforded after purification through silica gel chromatography (gradient, 25-40% ethyl actetate/petrol) the title compound *syn*-**479** (0.427 g, 2.12 mmol) in 31% yield as a white solid, *mp* 60-62°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3471 (br, OH), 1752 $(C=O)_{ox}$, 1696 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.91 (3H, t, *J* 7.5, CH_2CH_3), 1.13 (3H, d, *J* 7.0, $CHCH_3$),. 1.44 (2H, m, CH_2CH_3), 2.78 (1H, br s, O*H*), 3.79-3.89 (2H, m, C*H*OH, $CHCH_3$), 4.01-4.07 (2H, m, CH_2N), 4.37 (2H, app t, *J* 8.5, CH_2O); δ_C *($CDCl_3$)* 8.3, 8.5, 24.8, 39.6, 40.8, 60.1, 71.2, 151.4, 175.6; *m/z* (CI^+, *iso*-butane) 202 (100,

MH^+), 184 (95, M^+-OH), 143 (57%, M^+-CH_3CH_2CHOH); (Found (FAB$^+$) MH^+ 202.1080 $C_9H_{16}NO_4$ requires 202.1079); (Found C, 53.6; H, 7.45; N, 6.89. $C_9H_{15}NO_4$ requires C, 53.7; H, 7.51; N, 6.96%).

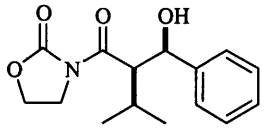
syn-3-(3-Hydroxy-2-isopropylpentanoyl)-1,3-oxazolidin-2-one 480[180]



syn-**480**

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (0.965 mg, 5.85 mmol) with a 1.0M solution of Bu_2BOTf in CH_2Cl_2 (7.02 mL, 7.02 mmol), *N,N*-diisopropylethylamine (1.43 mL, 8.19 mmol) and propionaldehyde (0.47 mL, 6.44 mmol) in CH_2Cl_2 (30 mL), according to general protocol F, afforded after purification through silica gel chromatography (gradient, 25-40% ethyl acetate/petrol) the title compound *syn*-**480** (0.644 g, 2.81 mmol) in 48% yield as a white solid, *mp* 60-62°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3463 (br, OH), 1752 $(C{=}O)_{ox}$, 1696 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.85 (3H, d, *J* 7.0, $CH(CH_3)_2$), 0.91 (3H, d, *J* 7.0, $CH(CH_3)_2$), 0.91 (3H, t, *J* 7.5, CH_2CH_3), 1.35 (1H, dqd, *J* 14.0, 10.0, 7.5, $CH_AH_BCH_3$), 1.51 (1H, dqd, *J* 14.0, 7.5, 2.3, $CH_AH_BCH_3$), 2.12 (1H, d of septets, *J* 8.0, 7.0, $CH(CH_3)_2$), 2.54 (1H, br s, O*H*), 3.83 (1H, app t, *J* 7.5, CH^iPr), 3.91-4.02 (3H, m, CH_2N, *CH*OH), 4.30-4.37 (2H, m, CH_2O); δ_C *($CDCl_3$)* 9.7, 19.2, 19.9, 24.4, 27.0, 41.8, 53.1, 60.8, 72.1, 153.3, 173.6; *m/z* (CI^+, *iso*-butane) 230 (5, MH^+), 212 (8, M^+-OH), 171 (34%, M^+-CH_3CH_2CHOH); (Found (FAB$^+$) MH^+ 230.1394 $C_{11}H_{20}NO_4$ requires 230.1392).

***syn*-3-{2-[Hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 481**

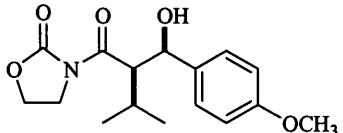


syn-**481**

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (0.993 g, 5.81 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (11.7 mL, 5.85 mmol), *N,N*-diisopropylethylamine (1.40 mL, 8.19 mmol) and benzaldehyde (0.65 mL, 6.43 mmol) in CH_2Cl_2 (30 mL), according to general protocol G, afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound *syn*-**481** (0.811 g, 2.93 mmol) in 50% yield as a white solid, *mp* 93-95°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3450 (s, OH), 1751

$(C=O)_{ox}$, 1695 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.01 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.08 (3H, d, *J* 7.0, $CH(CH_3)_2$), 2.36 (1H, septet of d, *J* 7.0, 5.5, $CH(CH_3)_2$), 2.41 (1H, d, *J* 3.0, O*H*), 3.62 (1H, ddd, *J* 11.0, 9.5, 7.0, CH_AH_BN), 3.84 (1H, ddd, *J* 11.0, 9.5, 7.0, CH_AH_BN), 4.07 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.24 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.48 (1H, dd, *J* 8.0, 5.5, C*H*^{i}Pr), 5.01 (1H, dd, *J* 8.0, 2.6, C*H*OH), 7.25-7.40 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 18.0, 19.8, 27.1, 41.3, 53.0, 60.3, 72.9, 125.6, 126.7, 127.1, 140.9, 152.0, 172.7; *m/z* (CI^+, NH_3) 295 (8, MNH_4^+), 278 (5, MH^+), 260 (28, M^+-OH), 234 (9, M^+-^{i}Pr), 105 (100%); (Found (ES^+) MNH_4^+ 295.1653 $C_{15}H_{23}N_2O_4$ requires 295.1652).

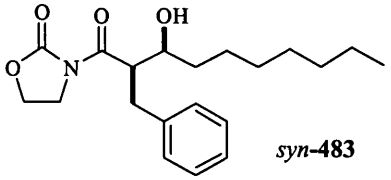
s*yn*-3-{2-[Hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 482



syn-**482**

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (1.500 g, 8.77 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (21.10 mL, 10.53 mmol), *N,N*-diisopropylethylamine (1.99 mL, 11.40 mmol) and *p*-anisaldehyde (1.17 mL, 9.65 mmol) in CH_2Cl_2 (40 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 10-20% ethyl acetate/petrol) the title compound *syn*-**482** (1.592 g, 5.18 mmol) in 60% yield as a white crystalline solid, *mp* 117-118°C; ν_{max} *(KBr disc)/cm^{-1}* 3449 (s, OH), 2838 $(C\text{-}H)_{MeO}$, 1755 $(C=O)_{ox}$, 1691 $(C=O)_{am}$, 1610 $(C=C)_{ar}$, 1582 $(C=C)_{ar}$, 1510 $(C=C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.02 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.08 (3H, d, *J* 7.0, $CH(CH_3)_2$), 2.24 (1H, d, *J* 3.5, O*H*), 2.35 (1H, septet of d, *J* 7.0, 5.5, $CH(CH_3)_2$), 3.65 (1H, ddd, *J* 11.0, 9.5, 7.0, CH_AH_BN), 3.79 (3H, s, $ArOCH_3$), 3.86 (1H, ddd, *J* 11.0, 9.5, 7.0, CH_AH_BN), 4.12 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.26 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.48 (1H, dd, *J* 8.5, 5.5, C*H*^{i}Pr), 4.97 (1H, dd, *J* 8.5, 3.5, C*H*OH), 6.84 (2H, d, *J* 8.5, Ar-*H*), 7.30 (2H, d, *J* 8.5, Ar-*H*); δ_C *($CDCl_3$)* 19.5, 21.3, 28.7, 42.9, 54.5, 55.6, 61.8, 74.0, 114.0, 128.5, 134.6, 153.6, 159.6, 174.2; *m/z* ($EI^{+\cdot}$) 307 (12, $M^{+\cdot}$), 171 (28, $M^{+\cdot}$-ArCHOH$^{\cdot}$), 149 (100%); (Found ($EI^{+\cdot}$) $M^{+\cdot}$ 307.1426 $C_{16}H_{21}NO_5$ requires 307.1420).

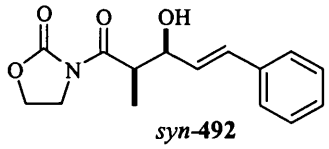
syn-3-(2-Benzyl-3-hydroxydecanoyl)-1,3-oxazolidin-2-one 483



syn-**483**

Reaction of 3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one **460** (0.500 g, 2.28 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (5.48 mL, 2.74 mmol), *N,N*-diisopropylethylamine (0.56 mL, 3.20 mmol) and octanal (0.39 mL, 2.51 mmol) in CH_2Cl_2 (10 mL), according to general protocol G, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound *syn*-**483** (0.582 g, 1.68 mmol) in 74% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3474 (br, OH), 1775 $(C=O)_{ox}$, 1695 $(C=O)_{am}$, 1603 $(C=C)_{ar}$, 1495 $(C=C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.81 (3H, t, *J* 7.0, CH_3), 1.16-1.28 (8H, m, Alk-*H*), 1.44-1.52 (4H, m, Alk-*H*), 2.65 (1H, br s, O*H*), 2.92 (1H, dd, *J* 13.0, 5.5, CH_AH_BPh), 2.99 (1H, dd, *J* 13.0, 10.0, CH_AH_BPh), 3.62 (1H, ddd, *J* 10.0, 9.0, 6.0, CH_AH_BN), 3.73-4.00 (3H, m, CH_AH_BN, CHOH, CH_AH_BO), 4.18 (1H, app dt, *J* 9.0, 6.0, CH_AH_BO), 4.33-4.40 (1H, m, $CHCH_2Ph$), 7.11-7.19 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 14.5, 23.0, 26.4, 29.6, 29.9, 32.2, 33.5, 34.4, 42.9, 49.5, 62.1, 72.6, 126.8, 128.7, 129.4, 139.3, 153.7, 175.9; *m/z* (CI^+, NH_3) 365 (11, MNH_4^+), 348 (13, MH^+), 237.2 (100%); (Found (ES^+) MH^+ 348.2171 $C_{20}H_{30}NO_4$ requires 348.2169).

syn-3-[(*E*)-3-Hydroxy-2-methyl-5-phenyl-4-pentenoyl]-1,3-oxazolidin-2-one 492

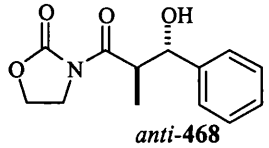


syn-**492**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **460** (0.500 g, 3.50 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.40 mL, 4.20 mmol), *N,N*-diisopropylethylamine (0.79 mL, 4.55 mmol) and *trans*-cinnamaldehyde (0.49 mL, 3.85 mmol) in CH_2Cl_2 (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-40% EtOAc/petrol) the title compound *syn*-**492** (0.841 g, 3.06 mmol) in 88% yield as a white crystalline solid, *mp* 100-101°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3476 (s, OH), 1762 $(C=O)_{ox}$, 1683 $(C=O)_{am}$, 1575 $(C=C)_{ar}$, 1494 $(C=C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.17 (3H, d, *J* 7.0, CH_3), 2.97 (1H, d, *J* 1.0, O*H*), 3.88-3.99 (3H, m, CH_2N, $CHCH_3$), 4.28-4.34 (2H, m, CH_2O), 4.58 (1H, ddd, *J* 6.0, 4.0, 1.3, CHOH), 6.14 (1H, dd, *J* 16.0, 6.0, HC=CHPh), 6.59 (1H, d, *J* 16.0, HC=CHPh), 7.15-7.34 (5H, m, Ph-*H*); δ_C

(CDCl$_3$) 11.6, 43.1, 43.1, 62.4, 73.2, 126.9, 128.1, 129.0 (3C), 131.8, 136.9, 153.8, 176.8; *m/z* (EI$^{+\cdot}$) 275 (7, $M^{+\cdot}$), 143 (42, $M^{+\cdot}$-PhCHCHCHOH$^{\cdot}$), 104.1 (100%); (Found (ES$^+$) MNH$_4^+$ 293.1495 $C_{15}H_{21}N_2O_4$ requires 293.1496).

anti-3-(3-Hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 468[153]



anti-**468**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.500 g, 3.50 mmol) with magnesium chloride (0.033 g, 0.35 mmol), triethylamine (0.97 mL, 6.99 mmol), benzaldehyde (0.43 mL, 4.19 mmol) and trimethylsilyl chloride (0.67 mL, 5.24 mmol) in ethyl acetate (7 mL), according to general protocol H, afforded after purification through silica gel chromatography (30% ethyl acetate/petrol) the title compound *anti*-**468** (0.290 g, 1.16 mmol) in 33% yield as a white crystalline solid, *mp* 102-104°C (lit.,[153] 107-107.5°C); ν_{max} *(KBr disc)/cm^{-1}* 3446 (s, OH), 1783 (C=O)$_{ox}$, 1665 (C=O)$_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 1.05 (3H, d, *J* 7.0, C*H*$_3$), 2.87 (1H, d, *J* 5.0, O*H*), 4.00-4.06 (2H, m, C*H*$_2$N), 4.28 (1H, dq, *J* 8.5, 7.0, C*H*CH$_3$), 4.36-4.45 (2H, m, C*H*$_2$O), 4.78 (1H, dd, *J* 8.5, 5.0, C*H*OH), 7.26-7.43 (5H, m, Ph-*H*); δ_C *(CDCl$_3$)* 15.2, 43.1, 44.8, 62.4, 77.5, 127.1, 128.5, 129.0, 142.1, 153.9, 176.9; *m/z* (CI$^+$, *NH$_3$*) 267 (94, MNH$_4^+$), 250 (48, MH$^+$), 105.1 (100%); (Found (ES$^+$) MH$^+$ 250.1079 $C_{13}H_{16}NO_4$ requires 250.1079).

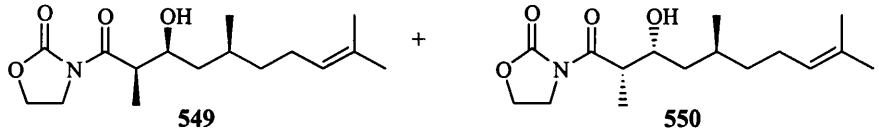
3-{(2*R*,3*R*)-3-Hydroxy-3-[(4*R*)-4-isopropenyl-1-cyclohexen-1-yl]-2-methylpropanoyl}-1,3-oxazolidin-2-one 545 and 3-{(2*S*,3*S*)-3-hydroxy-3-[(4*R*)-4-isopropenyl-1-cyclohexen-1-yl]-2-methylpropanoyl}-1,3-oxazolidin-2-one 546

545 + **546**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.500 g, 3.50 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.40 mL, 4.20 mmol), *N,N*-diisopropylethylamine (0.85 mL, 4.90 mmol) and L-(-)-perillaldehyde (0.60 mL, 3.85 mmol) in CH_2Cl_2 (20 mL), according to general protocol G, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound **545** + **546** (0.656 g, 2.24 mmol) in 64% yield as a white solid, which was a mixture of diastereomers, *mp* 87-

88°C ; ν_{max} *(KBr disc)/cm*$^{-1}$ 3495 (s, OH), 1769 (C=O)$_{ox}$, 1691 (C=O)$_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 1.13 (3H, d, *J* 6.0, C*H*$_3$, **545**), 1.15 (3H, d, *J* 6.0, C*H*$_3$, **546**), 1.38-1.55 (1H, m, Cy-*H*), 1.74 (3H, s, C*H*$_3$C=CH$_2$), 1.82-1.88 (1H, m, Cy-*H*), 1.92-2.06 (2H, m, Cy-*H*), 2.11-2.24 (2H, m, Cy-*H*), 2.76 (1H, s, O*H*, **545**), 2.78 (1H, s, O*H*, **546**), 3.75 (1H, m, Cy-*H*), 3.96-4.00 (1H, m, C*H*CH$_3$), 4.05 (2H, app t, *J* 8.0, C*H*$_2$N), 4.35-4.45 (1H, m, C*H*OH), 4.44 (2H, app t, *J* 8.0, C*H*$_2$O), 4.70-4.76 (2H, m, C*H*$_2$=C), 5.80-5.83 (1H, m, C*H*=C); δ_C *(CDCl$_3$)* 10.2, 10.9, 21.2, 21.3, 25.7, 26.0, 26.5, 27.7, 27.8, 30.6, 30.9, 40.4, 40.8, 41.2, 41.7, 43.1, 62.4, 68.4, 74.3, 74.6, 109.0, 109.1, 122.4, 123.0, 136.2, 136.7, 149.9, 150.2, 153.6, 177.5, 177.6; *m/z* (CI$^+$, NH$_3$) 311 (9, *M*NH$_4^+$), 294 (15, *M*H$^+$), 276 (40, *M*$^+$-OH), 161 (100), 144 (39%, *M*H$^+$-CHOHCy); (Found (CI, CH$_4$) *M*H$^+$ 294.1695 $C_{16}H_{24}NO_4$ requires 294.1700).

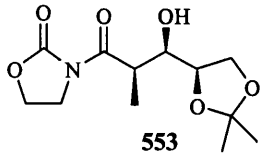
3-*(2R,3S,5S)*-3-Hydroxy-2,5,9-trimethyl-8-decenoyl)-1,3-oxazolidin-2-one 549 and 3-*(2S,3R,5S)*-3-hydroxy-2,5,9-trimethyl-8-decenoyl)-1,3-oxazolidin-2-one 550



549 **550**

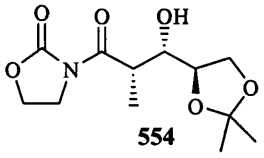
Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.300 g, 2.10 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (5.03 mL, 2.52 mmol), *N,N*-diisopropylethylamine (0.51 mL, 2.94 mmol) and *(S)*-citronellal (0.42 mL, 2.31 mmol) in CH_2Cl_2 (10 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound **549** + **550** (0.576 g, 1.94 mmol) in 93% yield as a low viscosity colourless oil, which was a mixture of diastereoisomers, ν_{max} *(neat)/cm*$^{-1}$ 3502 (br, OH), 1771 (C=O)$_{ox}$, 1695 (C=O)$_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 0.92 (3H, app t, *J* 7.0, C*H*$_3$, **549** + **550**), 1.05-1.28 (2H, m, Alk-H), 1.20 (3H, d, *J* 7.0, O=CCHC*H*$_3$, **549**), 1.21 (3H, d, *J* 7.0, O=CCHC*H*$_3$, **550**), 1.30-1.48 (2H, m, Alk-*H*), 1.60 (3H, s, CH=CC*H*$_3$), 1.68 (3H, s, CH=CC*H*$_3$), 1.54-1.70 (1H, m, CH$_2$C*H*CH$_3$), 1.92-2.08 (2H, m, C*H*$_2$CH=C(CH$_3$)$_2$), 2.73 (1H, d, *J* 2.3, O*H*, **549**), 2.80 (1H, d, *J* 3.0, O*H*, **550**), 3.73-3.83 (1H, m, O=CC*H*CH$_3$), 4.00-4.11 (3H, m, C*H*OH, CH$_2$N), 4.44 (2H, app t, *J* 8.0, C*H*$_2$O), 5.10 (1H, t, *J* 7.0, C*H*=C(CH$_3$)$_2$); δ_C *(CDCl$_3$)* 10.6, 11.0, 18.1, 19.3, 20.6, 25.7, 25.9, 26.0, 26.1 (2C), 29.3, 29.6, 36.9, 38.3, 41.4, 41.5, 42.2, 42.9, 43.0, 62.3, 68.4, 69.6, 69.8, 125.1, 131.6, 131.6, 153.6, 153.6, 177.9, 178.0; *m/z* (EI$^+$) 297.2 (11, *M*$^{+\cdot}$), 143 (100%, *M*$^{+\cdot}$-(CH$_3$)$_2$C=CHCH$_2$CH$_2$CH(CH$_3$)CH$_2$CHOH$^{\cdot}$); (Found (ES$^+$) *M*$^+$ 298.2009 $C_{16}H_{28}NO_4$ requires 298.2013).

***(2R,3R)*-3-{3-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-methylpropanoyl}-1,3-oxazolidin-2-one 553 and *(2S,3S)*-3-{3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-methylpropanoyl}-1,3-oxazolidin-2-one 554**



553

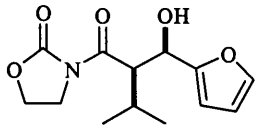
+



554

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.200 g, 1.40 mmol) with a 0.5M solution of 9-BBN.OTf in CH_2Cl_2 (3.36 mL, 1.68 mmol), *N,N*-diisopropylethylamine (0.34 mL, 1.96 mmol) and *(R)*-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (0.19 mL, 1.54 mmol) in hexanes (7 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 40-50% ethyl acetate/petrol) the title compound **553** + **554** (0.222 g, 0.81 mmol) in 58% as a thick colourless oil, which was a 2:1 mixture of diastereoisomers, ν_{max} *(neat)/cm*$^{-1}$ 3447 (br, OH), 1771 $(C{=}O)_{ox}$, 1699 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.28 (3H, d, *J* 6.5, CH=CCH_3, **553**), 1.34 (3H, s, CH_3), 1.38 (3H, d, *J* 6.5, CH=CCH_3, **554**), 1.43 (3H, s, CH_3), 2.55 (1H, d, *J* 6.5, O*H*, **553**), 3.11 (1H, d, *J* 3.0, O*H*, **554**), 3.72-4.18 (5H, m, C*H*OH, C*H*CH_3, CH_2, C*H*(O)), 4.05 (2H, app t, *J* 7.5, CH_2N), 4.44 (2H, app t, *J* 7.5, CH_2O); δ_C *($CDCl_3$)* 11.2, 12.1, 25.6, 25.8, 26.8, 27.1, 39.5, 41.3, 43.1, 62.3, 62.4, 66.6, 67.8, 68.4, 72.0, 73.1, 75.6, 77.2, 109.8, 110.1, 153.2, 153.6, 175.6, 178.0; *m/z* (CI^+, NH_3) 291 (30%, *M*NH_4^+), 274 (46, *M*H^+), 256 (5, *M*$^+$-OH), 230 (20, *M*H^+-CO_2), 144 (13, *M*H^+-CHOHR), 105.0 (100%); (Found (ES^+) *M*H^+ 274.1282 $C_{12}H_{20}NO_6$ requires 274.1285).

***syn*-3-{2-[2-Furyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 557**

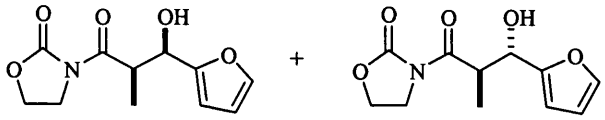


syn-**557**

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (0.500 g, 2.92 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (7.02 mL, 3.51 mmol), *N,N*-diisopropylethylamine (0.66 mL, 3.80 mmol) and 2-furaldehyde (0.27 mL, 3.22 mmol) in CH_2Cl_2 (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound *syn*-**557** (0.292 g, 1.09 mmol) in 38% yield, *mp* 96-98°C ; ν_{max} *(KBr disc)/cm*$^{-1}$ 3446 (s, OH), 1769 $(C{=}O)_{ox}$, 1676 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.97 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.99 (3H, d, *J* 7.0,

$CH(CH_3)_2$), 2.25 (1H, app octet, *J* 7.0, $CH(CH_3)_2$), 2.35 (1H, br s, O*H*), 3.81 (1H, ddd, *J* 11.0, 9.0, 7.5, CH_AH_BN), 3.89 (1H, ddd, *J* 11.0, 9.0, 6.5, CH_AH_BN), 4.24 (1H, app dt, *J* 9.0, 6.5, CH_AH_BO), 4.29 (1H, app dt, *J* 9.0, 7.5, CH_AH_BO), 4.44 (1H, dd, *J* 8.5, 6.5, C*H*^{i}Pr), 5.03 (1H, d, *J* 8.5, C*H*OH), 6.24 (2H, d, *J* 1.3, fur-*H*), 7.29 (1H, app t, *J* 1.3, fur-*H*); δ_C *(CDCl3)* 19.7, 20.7, 28.6, 43.0, 52.5, 62.1, 68.0, 107.3, 110.8, 142.4, 154.0, 155.1, 173.7; *m/z* (CI^+, NH_3) 285 (44, MNH_4^+), 267 (42, M^+), 189 (100%, M^+-fur); (Found (ES^+) MNH_4^+ 285.1447 $C_{13}H_{21}N_2O_5$ requires 285.1445).

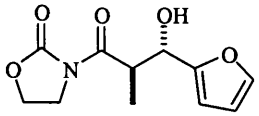
syn-3-[3-(2-Furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one 560 and _anti_-3-[3-(2-furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one 561



syn-**560** *anti*-**561**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.500 g, 3.50 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.40 mL, 4.20 mmol), *N,N*-diisopropylethylamine (0.85 mL, 4.90 mmol) and 2-furaldehyde (0.32 mL, 3.85 mmol) in CH_2Cl_2 (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound *syn*-**560** (0.162 g, 0.68 mmol) in 19% yield as a pale yellow solid, *mp* 77-79°C ; ν_{max} *(KBr disc)/cm*$^{-1}$ 3399 (br, OH), 1773 $(C=O)_{ox}$, 1681 $(C=O)_{am}$, 1506 $(C=C)_{ar}$; δ_H *(300MHz, CDCl3, Me4Si)* 1.12 (3H, d, *J* 7.0, CH_3), 2.96 (1H, d, *J* 3.5, O*H*), 3.82-3.90 (2H, m, CH_2N), 4.07 (1H, qd, *J* 7.0, 4.5, $CHCH_3$), 4.23-4.30 (2H, m, CH_2O), 4.95 (1H, app t, *J* 4.0, C*H*OH), 6.15-6.20 (2H, m, fur-*H*), 7.21 (1H, dd, *J* 1.7, 0.8, fur-*H*); δ_C *(CDCl3)* 12.2, 42.6, 43.0, 62.4, 69.1, 107.1, 110.6, 142.3, 153.4, 154.4, 176.6; *m/z* ($EI^{+\cdot}$) 239 (44, $M^{+\cdot}$), 143 (42, $M^{+\cdot}$-CHOHfur$^{\cdot}$), 84 (100%); (Found (ES^+) MH^+ 240.0867 $C_{11}H_{14}NO_5$ requires 240.0866) and the *anti*-aldolate **561** (0.032 g, 0.13 mmol) in 4% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3459 (br, OH), 1776 $(C=O)_{ox}$, 1693 $(C=O)_{am}$; δ_H *(300MHz, CDCl3, Me4Si)* 1.03 (3H, d, *J* 7.0, CH_3), 3.11 (1H, br s, O*H*), 3.98 (2H, m, CH_2N), 4.30 (1H, dq, *J* 8.5, 7.0, $CHCH_3$), 4.36 (2H, app t, *J* 8.0, CH_2O), 4.76 (1H, d, *J* 8.5, C*H*OH), 6.25-6.28 (2H, m, fur-*H*), 7.32-7.33 (1H, m, fur-*H*); δ_C *(CDCl3)* 14.9, 42.8, 43.1, 62.5, 70.6, 108.1, 110.6, 142.8, 153.9, 154.5, 176.5; *m/z* ($EI^{+\cdot}$) 239 (17, $M^{+\cdot}$), 143 (100, $M^{+\cdot}$-CHOHfur$^{\cdot}$); (Found (ES^+) MH^+ 240.0867 $C_{11}H_{14}NO_5$ requires 240.0866).

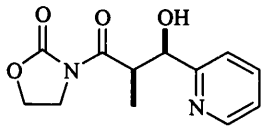
anti-3-[3-(2-Furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one 561



anti-**561**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.500 g, 3.50 mmol) with magnesium chloride (0.033 g, 0.35 mmol), triethylamine (0.97 mL, 6.99 mmol), sodium hexafluoroantimonate (0.271 g, 1.05 mmol), 2-furaldehyde (0.35 mL, 4.19 mmol) and trimethylsilyl chloride (0.67 mL, 5.24 mmol) in ethyl acetate (7 mL), according to general protocol I, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound *anti*-**561** (0.639 g, 2.67 mmol) in 77% yield as a colourless oil. Spectroscopic data were consistent with the spectroscopic data reported in the previous paragraph.

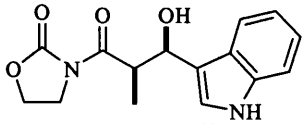
syn-3-[3-Hydroxy-2-methyl-3-(2-pyridinyl)propanoyl]-1,3-oxazolidin-2-one 564



syn-**564**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.480 g, 3.36 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.06 mL, 4.02 mmol), *N,N*-diisopropylethylamine (0.82 mL, 4.70 mmol) and 2-pyridinecarboxaldehyde (0.35 mL, 3.70 mmol) in CH_2Cl_2 (15 mL), according to general protocol G, afforded after purification through alumina gel chromatography (gradient, 40-100% ethyl acetate/petrol) the title compound *syn*-**564** (0.225 g, 0.90 mmol) in 27% yield as a yellow oil, ν_{max} *(neat)/cm*$^{-1}$ 3544 (OH), 1772 $(C{=}O)_{ox}$, 1700 $(C{=}O)_{am}$, 1593 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.87 (3H, d, *J* 7.0, CH_3), 4.04 (2H, app t, *J* 8.0, CH_2N), 4.06 (1H, qd, *J* 7.0, 2.5, $CHCH_3$), 4.35-4.43 (2H, m, CH_2O), 5.19 (1H, d, *J* 2.5, CHOH), 7.14-7.20 (1H, m, Pyr-*H*), 7.49 (1H, d, *J* 8.0, Pyr-*H*), 7.66 (1H, app dt, *J* 8.0, 1.6, Pyr-*H*), 8.47 (1H, d, *J* 5.0, Pyr-*H*); δ_C *($CDCl_3$)* 9.1, 43.3, 44.9, 62.6, 72.5, 121.3, 123.0, 137.4, 148.2, 154.0, 159.3, 175.3; *m/z* (CI^+, *iso*-butane) 251 (32, MH^+), 108 (100%); (Found (ES^+) MH^+ 251.1029 $C_{12}H_{15}N_2O_4$ requires 251.1026).

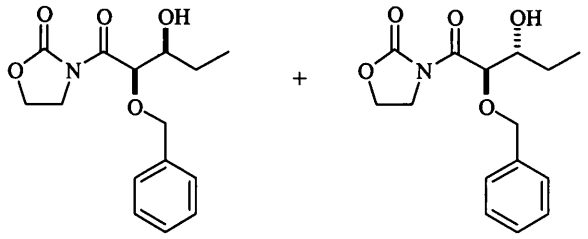
syn-3-[3-Hydroxy-3-(1*H*-indol-3-yl)-2-methylpropanoyl]-1,3-oxazolidin-2-one 568



syn-**568**

Reaction of 3-propionyl-1,3-oxazolidin-2-one **457** (0.485 g, 3.39 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.39 mL, 4.19 mmol), *N,N*-diisopropylethylamine (0.85 mL, 4.90 mmol) and 3-indolecarboxaldehyde (0.558 g, 3.84 mmol) pre-dissolved in 10 mL of THF, according to general protocol G, afforded after recrystallisation from ethyl acetate the title compound *syn*-**568** (0.450 g, 1.56 mmol) in 46% yield as a white solid, *mp* 147-149°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3454 (s, indole N-H), 3307 (s, OH), 1778 $(C{=}O)_{ox}$, 1078 $(C{=}O)_{am}$; δ_H *(300MHz, CD_3COCD_3, Me_4Si)* 1.21 (3H, d, *J* 7.0, CH_3), 3.76 (1H, ddd, *J* 10.5, 9.0, 6.0, CH_AH_BN), 3.97 (1H, ddd, *J* 10.5, 9.0, 7.5, CH_AH_BN), 4.03 (1H, d, *J* 4.5, O*H*), 4.21 (1H, app dt, *J* 9.0, 7.5, CH_AH_BO), 4.35-4.45 (2H, m, $CHCH_3$, CH_AH_BO), 5.36 (1H, app. t, *J* 5.0, C*H*OH), 6.99 (1H, ddd, *J* 8.0, 7.0, 1.1, Ph-*H*), 7.08 (1H, ddd, *J* 8.0, 7.0, 1.1, Ph-*H*), 7.27 (1H, d, *J* 1.8, C*H*NH), 7.37 (1H, d, *J* 8.0, Ph-*H*), 7.78 (1H, d, *J* 8.0, Ph-*H*) , 10.06 (1H, br s, NH_{ind}); δ_C *($CDCl_3$)* 13.1, 44.1, 45.0, 63.4, 9.8, 112.4, 119.0, 119.9, 120.8, 122.5, 123.7, 127.3, 138.1, 154.8, 176.8; *m/z* ($EI^{+\cdot}$) 288 (41, $M^{+\cdot}$), 270 (39, $M^{+\cdot}$-H_2O), 227 (100%); (Found (ES^+) MNH_4^+ 306.1453 $C_{15}H_{20}N_3O_4$ requires 306.1448).

syn-3-[2-(Benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one 572 and *anti*-3-[2-(benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one 575

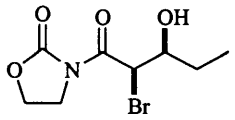


syn-**572** *anti*-**575**

Reaction of 3-[2-(benzyloxy)acetyl]-1,3-oxazolidin-2-one **571** (0.300 g, 1.28 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (3.06 mL, 1.53 mmol), *N,N*-diisopropylethylamine (0.31 mL, 1.79 mmol) and propionaldehyde (0.10 mL, 1.41 mmol) in CH_2Cl_2 (6 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-40% ethyl acetate/petrol) the title compound *syn*-**572** (0.187 g, 0.66 mmol) in 52% yield as a white solid, mp 93-95°C ; ν_{max} (KBr disc)/cm^{-1} 3509 (s, OH), 1773 $(C{=}O)_{ox}$, 1703 $(C{=}O)_{am}$, 1499 $(C{=}C)_{ar}$; δ_H *($300MHz$, $CDCl_3$, Me_4Si)*

0.87 (3H, t, *J* 7.5, CH_2CH_3), 1.53-1.66 (2H, m, CH_2CH_3), 2.15 (1H, br s, O*H*), 3.77 (1H, td, *J* 7.0, 2.5, C*H*OH), 3.95 (2H, app t, *J* 8.0, CH_2N), 4.36 (2H, app t, *J* 8.0, CH_2O), 4.38 (1H, d, *J* 11.0, OCH_AH_BPh), 4.64 (1H, d, *J* 11.0, OCH_AH_BPh), 5.06 (1H, d, *J* 2.5, C*H*OCH_2Ph), 7.22-7.31 (m, 5H, Ph-*H*); δ_C ($CDCl_3$) 10.4, 27.5, 42.9, 63.2, 73.3, 74.3, 79.3, 128.5, 128.8 (4C), 137.5, 153.9, 171.6; *m/z* (CI^+, NH_3) 311 (11, MNH_4^+), 294 (10, MH^+), 105 (100%); (Found (ES^+) MH^+ 294.1339 $C_{15}H_{20}NO_5$ requires 294.1336), and the title compound *anti*-**575** (0.032 g, 0.13 mmol) in 4% yield as a white solid, *mp* 96-97°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3440 (s, OH), 1785 $(C=O)_{ox}$, 1679 $(C=O)_{am}$; δ_H (300MHz, $CDCl_3$, Me_4Si) 0.92 (3H, t, *J* 7.5, CH_2CH_3), 1.45 (1H, dqd, *J* 14.0, 8.5, 7.5, $CH_AH_BCH_3$), 1.73 (1H, dqd, *J* 14.0, 7.5, 3.0, $CH_AH_BCH_3$), 2.08 (1H, d, *J* 9.0, O*H*), 3.66-3.74 (1H, m, C*H*OH), 3.90 (1H, ddd, *J* 11.0, 9.0, 7.0, CH_AH_BN), 3.78 (1H, ddd, *J* 11.0, 9.0, 7.0, CH_AH_BN), 4.26 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.33 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.49 (2H, s, CH_2Ph), 5.12 (1H, d, *J* 7.0, C*H*OCH_2Ph), 7.22-7.30 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 9.9, 27.0, 42.9, 63.0, 73.6, 74.6, 79.5, 128.5, 128.7, 129.0, 137.5, 154.4, 172.7; *m/z* ($EI^{+\cdot}$) 294 (2, $MH^{+\cdot}$), 217 (32, $MH^{+\cdot}$-Ph$^{\cdot}$), 187 (100%, $MH^{+\cdot}$-$PhCH_2O^{\cdot}$); (Found (ES^+) MH^+ 294.1340 $C_{15}H_{20}NO_5$ requires 294.1336).

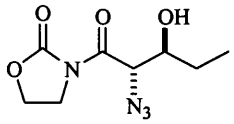
syn-3-(2-Bromo-3-hydroxypentanoyl)-1,3-oxazolidin-2-one 581



syn-**581**

Reaction of 3-(2-bromoacetyl)-1,3-oxazolidin-2-one **580** (1.000 g, 4.81 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (11.54 mL, 5.77 mmol), *N,N*-diisopropylethylamine (1.17 mL, 6.73 mmol) and propionaldehyde (0.38 mL, 5.29 mmol) in Et_2O (25 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound *syn*-**581** (0.468 g, 1.76 mmol) in 37% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3485 (br, OH), 1778 $(C=O)_{ox}$, 1703 $(C=O)_{am}$, 702 (s, C-Br); δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.94 (3H, t, *J* 7.5, CH_2CH_3), 1.44-1.71 (2H, m, CH_2CH_3), 3.12 (1H, br s, O*H*), 3.73-3.78 (1H, m, C*H*OH), 4.00-4.05 (2H, m, CH_2N), 4.40-4.45 (2H, m, CH_2O), 5.63 (1H, d, *J* 3.0, C*H*Br); δ_C *($CDCl_3$)* 10.2, 27.9, 43.1, 49.7, 62.7, 72.2, 152.9, 169.9; *m/z* (CI^+, *iso*-butane*)* 266-268 (58, M^+), 248-250 (100, M^+-OH), 207-209 (17, M^+-$CHOHCH_2CH_3$), 186 (47%, M^+-Br); (Found (ES^+) MH^+ 266.0025 $C_8H_{13}NO_4$ requires 266.0022).

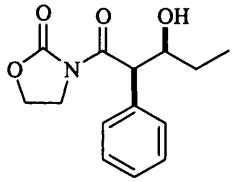
anti-3-(2-Azido-3-hydroxypentanoyl)-1,3-oxazolidin-2-one 587



anti-**587**

Sodium azide (0.070 g, 1.10 mmol) was added to a stirred solution of *syn*-aldolate **581** (0.058 mg, 0.22 mmol) in acetone (2 ml). Reaction mixture was refluxed for 3 hours and filtered to remove salts. The solvent was removed *in vacuo* to afford the title compound *anti*-**587** (0.039 g, 0.17 mmol) in 78% yield as a mixture of diastereoisomers (*anti*:*syn*, 83:17), ν_{max} *(neat)/cm*$^{-1}$ 3475 (br, OH), 2108 (N=N=N), 1778 $(C=O)_{ox}$, 1703 $(C=O)_{am}$, 1668 (C=N); δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.99 (3H, t, *J* 7.5, CH_2CH_3), 1.43-1.85 (2H, m, CH_2CH_3), 2.40 (1H, d, *J* 7.0, O*H*), 3.78-3.88 (1H, m, C*H*OH), 4.04 (2H, app t, *J* 8.0, CH_2N), 4.43 (2H, app t, *J* 8.0, CH_2O), 4.94 (1H, d, *J* 8.0, C*H*N_3, *anti*-isomer), 5.00 (1H, d, *J* 2.3, C*H*N_3, *syn*-isomer); δ_C *($CDCl_3$)* 8.3, 25.8, 41.7, 61.5, 61.6, 72.4, 152.7, 169.1; *m/z* (CI^+, NH_3) 246 (100, *M*NH_4^+), 229 (3, *M*H^+), 187 (59%, *M*H^+-N_3); (Found (ES^+) *M*NH_4^+ 246.1195 $C_8H_{16}N_5O_4O_2$ requires 246.1197).

syn-3-(3-Hydroxy-2-phenylpentanoyl)-1,3-oxazolidin-2-one 591

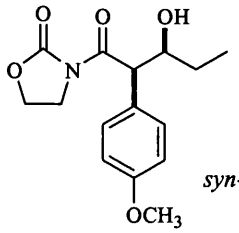


syn-**591**

Reaction of 3-(2-phenylacetyl)-1,3-oxazolidin-2-one **459** (0.994 g, 4.85 mmol) with a 1.0M solution of Bu_2BOTf in CH_2Cl_2 (5.86 mL, 5.86 mmol), *N,N*-diisopropylethylamine (1.20 mL, 6.83 mmol) and propionaldehyde (0.39 mL, 5.37 mmol) in CH_2Cl_2 (20 mL), according to general protocol F, afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound *syn*-**591** (0.464 g, 1.76 mmol) in 37% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3519 (br, OH), 1771 $(C=O)_{ox}$, 1694 $(C=O)_{am}$, 1601 $(C=C)_{ar}$, 1583 $(C=C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.99 (3H, t, *J* 7.5, CH_2CH_3), 1.35-1.48 (2H, m, CH_2CH_3), 2.70 (1H, d, *J* 2.7, O*H*), 3.92 (1H, ddd, *J* 11.0, 9.5, 6.5, CH_AH_BN), 4.06 (1H, ddd, *J* 11.0, 9.5, 7.0, CH_AH_BN), 4.11-4.17 (1H, m, C*H*OH), 4.29 (1H, app dt, *J* 9.5, 7.0, CH_AH_BO), 4.38 (1H, app dt, *J* 9.5, 6.5, CH_AH_BO), 5.04 (1H, d, *J* 5.5, C*H*Ph), 7.26-7.44 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 10.5, 27.6, 42.9, 53.5, 62.0, 74.0,

128.1, 128.7, 130.3, 134.2, 153.0, 174.2; *m/z* (CI^+, NH_3) 281 (20, MNH_4^+), 264 (19, MH^+), 223 (100%); (Found (ES^+) MH^+ 264.1227 $C_{14}H_{18}NO_4$ requires 264.1230).

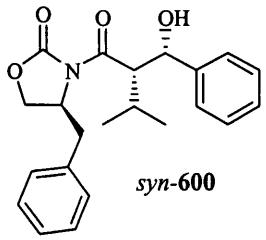
syn-3-[3-Hydroxy-2-(4-methoxyphenyl)pentanoyl]-1,3-oxazolidin-2-one 594



syn-**594**

Reaction of 3-[2-(4-methoxyphenyl)acetyl]-1,3-oxazolidin-2-one **593** (0.300 g, 1.28 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (3.06 mL, 1.53 mmol), *N,N*-diisopropylethylamine (0.31 mL, 1.79 mmol) and propionaldehyde (0.10 mL, 1.41 mmol) in CH_2Cl_2 (5 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-40% ethyl acetate/petrol) the title compound *syn*-**594** (0.288 g, 0.98 mmol) in 77% yield as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3504 (br, NH, OH), 2837 $(C\text{-}H)_{MeO}$, 1773 $(C{=}O)_{ox}$, 1683 $(C{=}O)_{ar}$, 1609 $(C{=}C)_{ar}$, 1507 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.91 (3H, t, *J* 7.5, CH_2CH_3), 1.23-1.37 (1H, m, $CH_AH_BCH_3$), 1.39 (1H, dqd, *J* 14.0, 7.5, 4.5, $CH_AH_BCH_3$), 2.52 (1H, br s, O*H*), 3.71 (3H, s, $ArOCH_3$), 3.83 (1H, ddd, *J* 11.0, 9.0, 6.5, CH_AH_BN), 3.96 (1H, ddd, *J* 11.0, 9.0, 7.0, CH_AH_BN), 4.05 (1H, ddd, *J* 8.0, 5.5, 4.5, C*H*OH), 4.20 (1H, app dt, *J* 9.0, 7.0, CH_AH_BO), 4.29 (1H, app dt, *J* 9.0, 6.5, CH_AH_BO), 4.89 (1H, d, *J* 5.5, C*H*Ar), 6.78 (2H, d, *J* 9.0, Ar-*H*), 7.26 (2H, d, *J* 9.0, Ar-*H*); δ_C *($CDCl_3$)* 10.6, 27.7, 43.0, 52.8, 55.6, 62.1, 74.0, 114.3, 126.3 , 131.5, 153.1, 159.6, 174.6; *m/z* (CI^+, NH_3) 311 (13, MNH_4^+), 294 (15, MH^+), 105.1 (100%); (Found (ES^+) MH^+ 294.1334 $C_{15}H_{20}NO_5$ requires 294.1336).

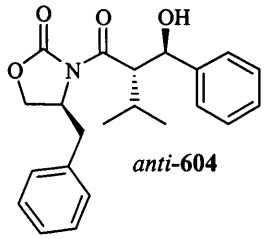
(4S)-4-Benzyl-3-[(2S,3S)-3-hydroxy-2-methyl-3-phenylpropanoyl]-1,3-oxazolidin-2-one 600



syn-**600**

Reaction of *(4S)*-4-benzyl-3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **472** (0.700 g, 2.68 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (7.00 mL, 3.50 mmol), *N,N*-diisopropylethylamine (0.64 mL, 3.66 mmol) and benzaldehyde (0.3 mL, 2.95 mmol) in CH_2Cl_2 (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (10% ethyl acetate/petrol) the title compound *syn*-**600** (0.634 g, 1.73 mmol) in 65% yield as a colourless oil, $[\alpha]_D^{25}$ +67.2 (c 2.84, CH_2Cl_2); ν_{max} *(neat)/cm*$^{-1}$ 3471 (br s, OH), 1779 $(C=O)_{ox}$, 1693 $(C=O)_{am}$, 1604 $(C=C)_{ar}$, 1493 $(C=C)_{ar}$; δ_H (300MHz, $CDCl_3$, Me_4Si) 1.09 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.16 (3H, d, *J* 7.0, $CH(CH_3)_2$), 2.30 (1H, d, *J* 3.5, O*H*), 2.42 (1H, septet of d, *J* 7.0, 5.5, $CH(CH_3)_2$), 2.56 (1H, dd, *J* 13.0, 10.5, CH_AH_BPh), 3.24 (1H, dd, *J* 13.0, 3.5, CH_AH_BPh), 3.59 (1H, app t, *J* 8.5, CH_AH_BO), 3.92 (1H, dd, *J* 9.0, 2.3, CH_AH_BO), 4.19-4.27 (1H, m, C*H*N), 4.46 (1H, dd, *J* 8.5, 5.5, C*H*^{i}Pr), 5.00 (1H, dd, *J* 8.5, 3.5, C*H*OH), 7.16-7.40 (10H, m, Ph-*H*); δ_C *(CDCl$_3$)* 19.6, 21.3, 28.9, 38.5, 54.8, 55.9, 66.0, 74.8, 127.1, 127.7, 128.4, 128.7, 129.3, 129.7, 135.7, 142.6, 153.5, 174.0; *m/z* (CI^+, NH_3) 385 (17, MNH_4^+), 368 (8, MH^+), 279.2 (100%); (Found (ES^+) MH^+ 368.1858 $C_{22}H_{26}NO_4$ requires 368.1862).

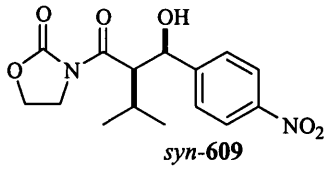
***anti-(4S)*-4-Benzyl-3-{*(2S)*-2-[(*R*)-hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 604**



anti-**604**

Reaction of (4*S*)-4-benzyl-3-[(2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropanoyl]-1,3-oxazolidin-2-one *syn*-**600** (0.100 g, 0.27 mmol) with a 1.0M solution of Et_2Zn in toluene (0.03 mL, 0.03 mmol) in CH_2Cl_2 (2mL), according to general protocol J, gave a mixture of *N*-acyl oxazolidin-2-one **472** (20%), *syn*-aldolate **600** (< 10%) and the title compound **604** (70%). The crude mixture was purified by silica gel chromatography (gradient, 10-40% ethyl acetate/petrol) to afford the title compound *anti*-**604** (0.040 g, 0.11 mmol) in 40% yield and > 95% d.e. as a colourless oil, $[\alpha]_D^{25}$ +104 (c 1.61 in CH_2Cl_2); ν_{max} *(neat)/cm*$^{-1}$ 3501 (br, OH), 1779 $(C{=}O)_{ox}$, 1699 $(C{=}O)_{am}$, 1604 $(C{=}C)_{ar}$, 1495 $(C{=}C)_{ar}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.03 (3H, d, *J* 7.0, CH_3), 1.20 (3H, d, *J* 7.0, CH_3), 2.33 (1H, d of septets, *J* 9.5, 7.0, $CH(CH_3)_2$), 2.58 (1H, dd, *J* 13.5, 10.2, CH_AH_BPh), 3.22 (1H, dd, *J* 13.5, 3.5, CH_AH_BPh), 3.45 (1H, app t, *J* 8.1, CH_AH_BOH), 3.53 (1H, d, *J* 9.5, OH), 3.88 (1H, app dd, *J* 9.0, 2.0, CH_AH_BOH), 4.17-4.25 (1H, m, CH_2N), 4.22 (1H, dd, *J* 9.5, 4.5, CH^iPr), 5.08 (1H, dd, *J* 9.5, 4.5, *CH*Ph), 7.16-7.31 (10H, m, Ph-*H*); δ_C *($CDCl_3$)* 20.5, 21.1, 28.8, 38.3, 55.6, 55.9, 66.1, 72.8, 125.6, 127.7, 127.7, 128.6, 129.3, 129.7, 135.6, 143.0, 153.2, 176.6; *m/z* (CI^+, NH_3) 385 (7, MNH_4^+), 368 (11, MH^+), 324 (5, MH^+-CO_2), 195.1 (100%); (Found (ES^+) MH^+ 368.1857 $C_{22}H_{26}NO_4$ requires 368.1862).

syn-3-{2-[Hydroxy(4-nitrophenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 609



syn-**609**

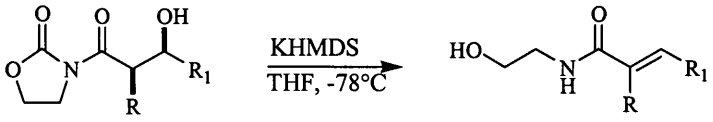
Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **458** (0.297 g, 1.74 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (4.21 mL, 2.11 mmol), *N,N*-diisopropylethylamine (0.40 mL, 2.28 mmol) and *p*-nitrobenzaldehyde (292 mg, 1.93 mmol) in CH_2Cl_2 (10 mL), according to general protocol G, afforded after purification

through silica gel chromatography (20% ethyl acetate/petrol) the title compound *syn*-**613** (0.393 g, 1.22 mmol) in 70% yield as a pale yellow solid, *mp* 108-110°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3408 (s, OH), 1744 $(C{=}O)_{ox}$, 1691 $(C{=}O)_{am}$, 1523 $(N{=}O)_{conj}$, 1352 $(N{=}O)_{conj}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.93 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.02 (3H, d, *J* 7.0, $CH(CH_3)_2$), 2.27 (1H, app octet, *J* 7.0, $CH(CH_3)_2$), 2.93 (1H, d, *J* 2.6, O*H*), 3.81 (1H, ddd, *J* 11.0, 9.0, 8.0, CH_AH_BN), 3.97 (1H, ddd, *J* 11.0, 9.0, 6.0, CH_AH_BN), 4.32 (1H, app dt, *J* 9.0, 6.0, CH_AH_BO), 4.37 (1H, app dt, *J* 9.0, 8.0, CH_AH_BO), 4.46 (1H, app t, *J* 6.0, C*H*^{i}Pr), 5.18 (1H, dd, *J* 6.0, 2.6, C*H*OH), 7.60 (2H, d, *J* 9.0, Ar-*H*), 8.19 (2H, d, *J* 9.0, Ar-*H*); δ_C *($CDCl_3$)* 20.1, 21.4, 28.3, 42.9, 54.4, 62.1, 73.0, 123.8, 127.9, 147.7, 149.7, 153.8, 174.4; *m/z* (CI^+, NH_3) 340 (100, MNH_4^+), 323 (10%, MH^+); (Found (ES^+) MNH_4^+ 340.1503 $C_{15}H_{22}N_3O_6$ requires 340.1503); (Found: C, 55.5; H, 5.50; N, 8.47. $C_{15}H_{18}N_2O_6$ requires C, 55.9; H, 5.63; N, 8.47%).

8.4 Preparation of α,β-unsaturated amides

Procedure for the elimination reaction with KHMDS:

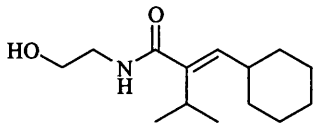
General protocol K



syn-**627** *(E)*-**631**

A 0.5M solution of KHMDS in toluene (1.5 eq.) was added dropwise to a stirred solution of *syn*-aldolate **627** (1 eq.) in THF at –78°C under nitrogen. The reaction was stirred at –78°C for two hours. Saturated NH_4Cl_{aq} was added and the reaction extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford α,β-unsaturated amide *(E)*-**631**.

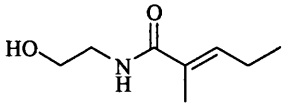
(*E*)-3-Cyclohexyl-*N*-(2-hydroxyethyl)-2-isopropyl-2-propenamide 478



(E)-**478**

Reaction of *syn*-3-{2-[cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **476** (0.100 g, 0.35 mmol) with a 0.5M solution of KHMDS in toluene (1.06 mL, 0.53 mmol) in THF (2 mL), according to general protocol K, gave the title compound *(E)*-**478** (0.075 g, 0.31 mmol) in 93% d.e. The crude product was purified for analysis by silica gel chromatography (gradient, 20-30% ethyl acetate/petrol), to afford the title compound *(E)*-**478** (0.064 g, 0.27 mmol) in 77% yield and > 95% d.e. as a white solid, *mp* 84-86°C ; ν_{max} *(KBr disc)/cm*$^{-1}$ 3291 (br, OH, NH), 1652 $(C=O)_{am}$, 1619 (C=C), 1541 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.01-1.37 (6H, m, Cy-H), 1.18 (6H, d, *J* 7.0, $CH(CH_3)_2$), 1.60-1.78 (4H, m, Cy-*H*), 2.25-2.39 (1H, m, Cy-*H*), 2.83 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 2.95 (1H, t, *J* 4.5, O*H*), 3.44 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.74 (2H, app q, *J* 5.5, 5.0, CH_2OH), 5.59 (1H, d, *J* 10.0, C*H*=C), 6.08 (1H, br s, N*H*); δ_C *($CDCl_3$)* 22.1 (2 C), 26.1 (2 C), 26.2, 28.6, 33.3 (2 C), 37.0, 42.9, 63.3, 137.9, 142.0, 173.1; *m/z* ($EI^{+\cdot}$) 239 (65, $M^{+\cdot}$), 224 (85, $M^{+\cdot}$-$CH_3^{\cdot}$), 179 (68%, $M^{+\cdot}$-$HOCH_2CH_2NH^{\cdot}$); (Found ($EI^{+\cdot}$) M^+ 239.1886 $C_{14}H_{25}NO_2$ requires 239.1885)

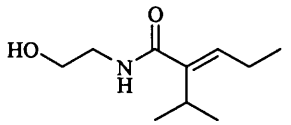
(*E*)-*N*-(2-Hydroxyethyl)-2-methyl-2-pentenamide 484



(E)-**484**

Reaction of *syn*-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one **479** (0.050 g, 0.25 mmol) with a 0.5M solution of KHMDS in toluene (0.75 mL, 0.37 mmol) in THF (3 mL), according to general protocol K, afforded the title compound *(E)*-**484** (0.026 g, 0.17 mmol) in 67% yield and > 95% d.e. as a white solid of low melting point, ν_{max} *(KBr disc)/cm*$^{-1}$ 3405 (br, OH, NH), 1701 $(C=O)_{am}$, 1615 (C=C), 1538 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.04 (3H, t, *J* 7.5, CH_2CH_3), 1.85 (3H, s, CH_3), 2.17 (2H, app pentet, *J* 7.5, CH_2CH_3), 2.86 (1H, br s, O*H*), 3.50 (2H, app q, *J* 6.0, 5.0, CH_2NH), 3.77 (2H, app t, *J* 5.0, CH_2OH), 6.19 (1H, s, N*H*), 6.38 (1H, t, *J* 7.5, *H*C=C); δ_C *($CDCl_3$)* 11.5, 12.2, 20.6, 41.7, 61.4, 128.7, 137.5, 169.7; *m/z* (CI^+, NH_3) 158 (100%, MH^+); (Found (ES) MH^+ 158.1179 $C_8H_{16}NO_2$ requires 158.1176).

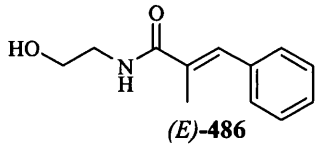
(*E*)-*N*-(2-Hydroxyethyl)-2-isopropyl-2-pentenamide 485



(E)-**485**

Reaction of *syn*-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one **480** (0.100 g, 0.44 mmol) with a 0.5M solution of KHMDS in toluene (1.30 mL, 0.65 mmol) in THF (3 mL), according to general protocol K, afforded the title compound *(E)*-**485** (0.080 g, 0.43 mmol) in 99% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3338 (br, OH, NH), 1653 $(C=O)_{am}$, 1617 (C=C), 1534 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.03 (3H, t, *J* 7.5, CH_2CH_3), 1.16 (6H, d, *J* 7.0, $CH(CH_3)_2$), 2.14 (2H, app pentet, *J* 7.5, CH_2CH_3), 2.81 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.43 (2H, app q, *J* 5.5, 4.5, CH_2NH), 3.50 (1H, br s, O*H*), 3.73 (2H, app t, *J* 5.0, CH_2OH), 5.77 (1H, t, *J* 7.5, *H*C=C), 6.26 (1H, br s, N*H*); δ_C *($CDCl_3$)* 13.2, 20.1, 20.7 (2C), 27.2, 41.7, 61.8, 133.0, 142.2, 171.9; *m/z* (CI^+, *iso*-butane) 186 (88, MH^+), 185 (32, M^+), 125 (100%, M^+-$HOCH_2CH_2NH$); (Found (FAB^+) MH^+ 186.1495 $C_{10}H_{20}NO_2$ requires 186.1494).

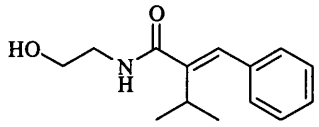
(*E*)-*N*-(2-Hydroxyethyl)-2-methyl-3-phenyl-2-propenamide 486



(E)-**486**

Reaction of *syn*-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one **467** (0.200 g, 0.80 mmol) with a 0.5M solution of KHMDS in toluene (2.41 mL, 1.20 mmol) in THF (4 mL), according to general protocol K, afforded the title compound *(E)*-**486** (0.143 g, 0.70 mmol) in 91% yield and > 95% d.e. as a white solid, *mp* 101-103°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3284 (br, OH, NH), 1644 $(C{=}O)_{am}$, 1620 (C=C), 1575 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 2.04 (3H, d, *J* 1.4, $CHC(CH_3)$), 3.08 (1H, br s, O*H*), 3.46-3.51 (2H, m, CH_2N), 3.74 (2H, app t, *J* 5.0, CH_2O), 6.48 (1H, br s, N*H*), 7.19 (1H, s, *H*C=C), 7.20-7.33 (5H, m, Ar-*H*); δ_C *($CDCl_3$)* 14.6, 43.3, 62.8, 128.3, 128.7, 129.7, 131.7, 135.0, 136.3, 171.2; *m/z* (CI^+, NH_3) 206 (100%, MH^+); (Found (ES^+) MH^+ 206.1177 $C_{12}H_{16}NO_2$ requires 206.1176).

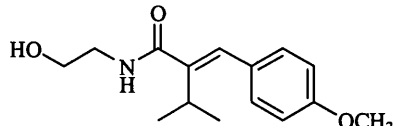
(*E*)-*N*-(2-Hydroxyethyl)-2-isopropyl-3-phenyl-2-propenamide 487



(E)-**487**

Reaction of s*yn*-3-{2-[hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **481** (0.085 g, 0.31 mmol) with a 0.5M solution of KHMDS in toluene (1.08 mL, 0.54 mmol) in THF (3 mL), according to general protocol K, afforded title compound *(E)*-**487** (0.068 g, 0.29 mmol) in 92% d.e. The crude product was purified for analysis by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound *(E)*-**487** (0.046 g, 0.20 mmol) in 69% yield and > 95% d.e. as a white solid, *mp* 101-103°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3317 (s, OH, NH), 1641 $(C{=}O)_{am}$, 1612 (C=C), 1538 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.24 (6H, d, *J* 7.0, $CH(CH_3)_2$), 2.95 (1H, br s, O*H*), 3.07 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.52 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.79 (2H, app t, *J* 5.0, CH_2OH), 6.33 (1H, br s, N*H*), 6.79 (1H, br s, *H*C=C), 7.25-7.39 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 21.9 (2C), 28.5, 42.8, 63.0, 128.0, 128.8, 129.1, 130.1, 136.1, 145.7, 172.4; *m/z* ($EI^{+\cdot}$) 233 (19, $M^{+\cdot}$), 173 (48, $M^{+\cdot}$- $HOCH_2CH_2NH^{\cdot}$), 145(57, $M^{+\cdot}$- $HOCH_2CH_2NHCO^{\cdot}$), 91 (100%, $PhCH_2^+$); (Found (ES^+) MH^+ 234.1489 $C_{14}H_{20}NO_2$ requires 234.1489).

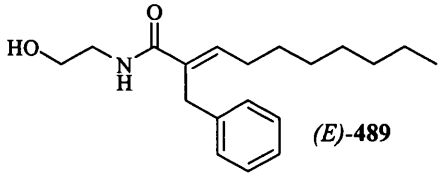
(*E*)-*N*-(2-Hydroxyethyl)-2-isopropyl-3-(4-methoxyphenyl)-2-propenamide 488



(E)-**488**

Reaction of *syn*-3-{2-[hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **482** (0.200 g, 0.65 mmol) with a 1.0M solution of KHMDS in toluene (1.95 mL, 0.98 mmol) in THF (4 mL), according to general protocol K, gave the title compound *(E)*-**488** (0.155 g, 0.59 mmol) in 90% d.e. The crude product was purified for analysis by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound *(E)*-**488** (0.110 g, 0.42 mmol) in 64% yield and > 95% d.e. as a white solid, *mp* 91-93°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3279 (s, OH), 3064 $(C{=}C)_{ar}$, 2834 $(C{-}H)_{MeO}$, 1645 $(C{=}O)_{am}$, 1620 (C=C), 1606 $(C{=}C)_{ar}$, 1542 $(C{=}O)_{am}$, 1510 $(C{=}C)_{ar}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 1.24 (6H, d, *J* 7.0, $CH(CH_3)_2$), 3.09 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.18 (1H, br s, O*H*), 3.50 (2H, app dt, *J* 5.5, 5.0, CH_2NH), 3.75-3.85 (2H, m, CH_2OH), 3.82 (3H, s, $ArOCH_3$), 6.38 (1H, br s, N*H*), 6.73 (1H, s, C*H*=C), 6.89 (2H, d, *J* 9.0, Ar-*H*), 7.21 (2H, d, *J* 8.5, Ar-*H*); δ_C *(CDCl$_3$)* 21.9 (2C), 28.4, 42.8, 55.7, 62.9, 114.2, 128.5, 129.7, 130.5, 144.1, 159.4, 172.6; *m/z* ($EI^{+\cdot}$) 263 (35, $M^{+\cdot}$), 203 (26, $M^{+\cdot}$-$HOCH_2CH_2NH^{\cdot}$), 84 (100%); (Found ($EI^{+\cdot}$) M^+ 263.1518 $C_{15}H_{21}NO_3$ requires 263.1521).

(*E*)-2-Benzyl-*N*-(2-hydroxyethyl)-2-decenamide 489

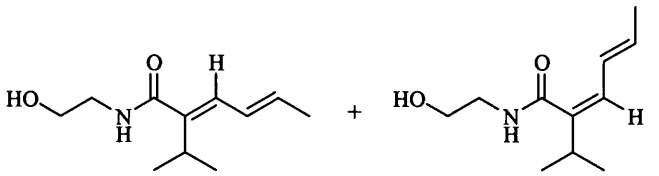


(E)-**489**

Reaction of *syn*-3-(2-benzyl-3-hydroxydecanoyl)-1,3-oxazolidin-2-one **483** (0.135 g, 0.39 mmol) with a 0.5M solution of KHMDS in toluene (1.17 mL, 0.58 mmol) in THF (3 mL), according to general protocol K, gave the title compound *(E)*-**489** (0.110 g, 0.36 mmol) in 92% d.e. The crude product was purified for analysis by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound *(E)*-**489** (0.086 g, 0.28 mmol) in 73% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3342 (br, OH, NH), 1656 $(C{=}O)_{am}$, 1620 (C=C), 1537 $(C{=}O)_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 0.88 (3H, t, *J* 7.0, CH_3), 1.23-1.28 (8H, m, Alk-*H*), 1.39-1.46 (2H, m, $CH_2CH_2CH{=}C$), 2.21 (2H, app q, *J* 7.5, $CH_2CH{=}C$), 2.97 (1H, br s, OH), 3.33 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.57 (2H, m, CH_2OH), 3.69 (2H, s, CH_2Ph), 6.17 (1H, br t, *J* 5.0, N*H*), 6.54 (1H, t, *J* 7.5, $HC{=}CCH_3$),

7.16-7.30 (5H, m, Ph-*H*); δ_C *(CDCl₃)* 14.5, 23.0, 28.9, 29.3, 29.5, 29.8, 32.1, 33.1, 43.1, 62.9, 126.8, 128.5, 129.1, 134.0, 139.0, 139.3, 170.5; *m/z* ($EI^{+\cdot}$) 303 (10, $M^{+\cdot}$), 243 (13, $M^{+\cdot}$-$HOCH_2CH_2NH^{\cdot}$), 91 (100%, $PhCH_2^+$); (Found (ES^+) MH^+ 304.2275 $C_{19}H_{30}NO_2$ requires 304.2271).

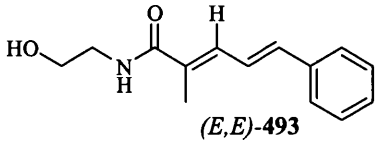
(2E,4E)-*N*-(2-Hydroxyethyl)-2-isopropyl-2,4-hexadienamide 490 and (2Z,4E)-*N*-(2-hydroxyethyl)-2-isopropyl-2,4-hexadienamide 491



(E,E)-**490** *(Z,E)*-**491**

Reaction of *syn*-3-[(*E*)-3-hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one **463** (0.200 g, 0.83 mmol) with a 0.5M solution of KHMDS in toluene (2.50 mL, 1.25 mmol) in THF (5 mL), according to general protocol K, gave the title compound *(E,E)*-**490** (0.153 g, 0.78 mmol) in 40% d.e. which was purified through silica (pre-coated with silver nitrate) gel chromatography to afford the title compound *(E,E)*-**490** (0.016 g, 0.08 mmol) in 10% yield as a pale oil, δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.20 (6H, d, *J* 7.0, $CH(CH_3)_2$), 1.83 (3H, dd, *J* 7.0, 1.5, $CH{=}CHCH_3$), 2.95 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.20 (1H, br s, O*H*), 3.45 (2H, app dt, *J* 5.5, 4.0, CH_2NH), 3.74 (2H, app t, *J* 5.0, CH_2OH), 5.89 (1H, dqd, *J* 13.0, 7.0, 1.5, $CHCH{=}CHCH_3$), 6.21 (1H, br s, N*H*), 6.33 (1H, br d, *J* 10.5, $CHCH{=}CHCH_3$), 6.39 (1H, ddq, *J* 13.0, 10.5, 1.5, $CHCH{=}CHCH_3$); δ_C *($CDCl_3$)* 19.0, 21.8 (2C), 28.6, 42.8, 63.0, 126.6, 130.6, 135.2, 141.0, 172.5; *m/z* ($EI^{+\cdot}$) 197 (23, $M^{+\cdot}$), 182 (33, $M^{+\cdot}$- $CH_3^{\cdot}$), 169 (38, $M^{+\cdot}$- $CH_3CH^{\cdot}$), 154 (100, $M^{+\cdot}$-$(CH_3)_2CH^{\cdot}$), 137 (28, $M^{+\cdot}$-$HO(CH_2)_2NH^{\cdot}$), 109 (43, $M^{+\cdot}$-$HO(CH_2)_2NHCO^{\cdot}$), and the geometric isomer *(Z,E)*-**491** (0.015 g, 0.08 mmol) in 9% yield, δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.08 (6H, d, *J* 7.0, $CH(CH_3)_2$), 1.77 (3H, dd, *J* 7.0, 1.5, $CH{=}CHCH_3$), 2.64 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.00 (1H, br s, O*H*), 3.53 (2H, app dt, *J* 5.6, 4.6, CH_2NH), 3.78 (2H, app t, *J* 5.0, CH_2OH), 5.79 (1H, dq, *J* 15.0, 7.0, $CHCH{=}CHCH_3$), 5.99 (1H, d, *J* 11.0, $CHCH{=}CHCH_3$), 6.13 (1H, br s, N*H*), 6.28 (1H, ddq, *J* 15.0, 11.0, 1.5, $CHCHCH_3$).

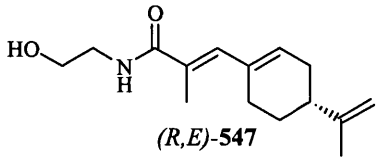
***(2E,4E)-N*-(2-hydroxyethyl)-2-methyl-5-phenyl-2,4-pentadienamide 493**



(E,E)-**493**

Reaction of *syn*-3-[(*E*)-3-hydroxy-2-methyl-5-phenyl-4-pentenoyl]-1,3-oxazolidin-2-one **492** (0.275 g, 1.00 mmol) with a 0.5M solution of KHMDS (3.00 mL, 1.50 mmol) in THF (5 mL), according to general protocol K, gave the title compound *(E)*-**493** (0.223 g, 0.97 mmol) in 60% d.e. The crude product was purified for analysis by recrystallisation from hot ethyl acetate, to afford the title compound *(E)*-**493** (0.147 g, 0.64 mmol) in 64% yield and >95% d.e. as a white solid, *mp* 141-142°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3293 (br, OH), 3250 (br, NH), 1642 $(C{=}O)_{am}$, 1585 (C=C), 1542 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 2.08 (3H, s, CH_3), 2.87 (1H, t, *J* 5.0, O*H*), 3.55 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.80 (2H, app q, *J* 5.0, 5.0, CH_2OH), 6.32 (1H, br s, N*H*), 6.83 (1H, d, *J* 15.0, C*H*CH=CHPh), 7.01 (1H, d, *J* 11.5, CHCH=C*H*Ph), 7.10 (1H, dd, *J* 15.0, 11.0, CHC*H*=CHPh), 7.28-7.48 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 13.6, 43.3, 63.1, 124.0, 127.3, 128.9, 129.1, 129.9, 134.9, 137.0, 138.6, 170.5; *m/z* ($EI^{+\cdot}$) 231 (33, $M^{+\cdot}$), 171 (80, $MH^{+\cdot}$-$HOCH_2CH_2NH^{\cdot}$), 154 (78, $M^{+\cdot}$- $Ph^{\cdot}$), 141 (47, $M^{+\cdot}$- $PhCH^{\cdot}$), 128 (100, $M^{+\cdot}$- $PhCHCH^{\cdot}$), 115 (38%, $M^{+\cdot}$- $PhCHCHCH^{\cdot}$); (Found (ES^+) MH^+ 232.1330 $C_{14}H_{18}NO_2$ requires 232.1332).

***(E)*-*N*-(2-Hydroxyethyl)-3-[*(4R)*-4-isopropenyl-1-cyclohexen-1-yl]-2-methyl-2-propenamide 547**

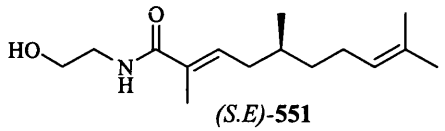


(R,E)-**547**

Reaction of aldolates **545** + **546** (0.100 g, 0.34 mmol) with a 0.5M solution of KHMDS in toluene (2.05 mL, 1.02 mmol) in THF (4 mL), according to general protocol K, gave the title compound *(R,E)*-**547** in 50% d.e. The crude mixture was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound *(R,E)*-**547** (0.043 mg, 0.17 mmol) in 51% isolated yield and > 95% d.e. as a white solid, $[\alpha]_D^{25}$ -72.2 (c 0.90, CH_2Cl_2); *mp* 67-69°C ; ν_{max} *(KBr disc)/cm*$^{-1}$ 3300 (br, NH), 3292 (s, OH), 1634 $(C{=}O)_{am}$, 1603 (C=C), 1538 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.35-1.48 (1H, m, Cy-*H*), 1.68 (3H, s, $H_3CC{=}CH_2$), 1.75-1.84 (1H, m, Cy-*H*), 1.95 (3H, s, $CH_3C{=}CH$), 2.00-2.11 (2H, m, Cy-*H*), 2.16-2.24 (3H, m, Cy-*H*), 3.28 (1H, s, O*H*), 3.42 (2H, app q, *J* 5.5, 5.0, CH_2NH),

3.68 (2H, app t, *J* 5.0, C*H*$_2$OH), 4.67 (2H, d, *J* 7.0, C=C*H*$_2$), 5.76 (1H, m, C=C*H*CH$_2$), 6.33 (1H, br s, N*H*), 6.66 (1H, s, CH$_3$C=C*H*); δ_C *(CDCl$_3$)* 14.7, 21.2, 28.0, 29.4, 31.6, 40.8, 43.3, 62.9, 109.3, 128.5, 131.5, 134.6, 137.4, 149.7, 171.8; *m/z* (EI$^+$) 249 (16, M^+), 208 (11, M^+- CH$_3$CH(CH$_2$)$^\cdot$), 189 (10%, M^+- OHCH$_2$CH$_2$NH$^\cdot$), 121 (55%, Cy$^+$), 91 (100%); (Found (ES$^+$) MH$^+$ 250.1802 $C_{15}H_{24}NO_2$ requires 250.1802).

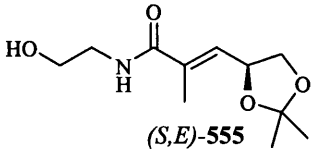
***(2E,5S)-N*-(2-hydroxyethyl)-2,5,9-trimethyl-2,8-decadienamide 551**



(S.E)-**551**

Reaction of aldolates **549** + **550** (0.150 mg, 0.51 mmol) with a 0.5M solution of KHMDS in toluene (1.52 mL, 0.76 mmol) in THF (3 mL), according to general protocol K, gave the title compound *(S,E)*-**551** (0.121 mg, 0.48 mmol) in 60% d.e. The crude product was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound *(S,E)*-**551** (0.071 g, 0.28 mmol) in 55% yield and > 95% d.e. as a colourless oil, $[\alpha]_D^{25}$ +2.7 (c 2.61, CH_2Cl_2), ν_{max} *(neat)/cm^{-1}* 3402 (br, OH, NH), 1657 (C=O)$_{am}$, 1615 (C=C), 1538 (C=O)$_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 0.90 (3H, d, *J* 6.5, CHC*H*$_3$), 1.12-1.27 (1H, m, C*H*$_A$H$_B$CH$_2$CH=C(CH$_3$)$_2$), 1.30-1.42 (1H, m, CH$_A$*H*$_B$CH$_2$CH=C(CH$_3$)$_2$), 1.55-1.65 (1H, m, C*H*CH$_3$), 1.60 (3H, s, CH=C(C*H*$_3$)$_2$), 1.68 (3H, s, CH=C(C*H*$_3$)$_2$), 1.85 (3H, s, CH=CC*H*$_3$), 1.90-2.05 (2H, m, CH$_2$C*H*$_2$CH=C(CH$_3$)$_2$), 2.10-2.19 (2H, m, C*H*$_2$CH=CCH$_3$), 3.48 (2H, app q, *J* 5.5, 5.0, C*H*$_2$NH), 3.61 (1H, br s, O*H*), 3.72-3.76 (2H, m, C*H*$_2$OH), 5.07 (1H, t, *J* 7.0, C*H*=C(CH$_3$)$_2$), 6.41 (1H, br s, N*H*), 6.44 (1H, t, *J* 6.5, C*H*=C); δ_C *(CDCl$_3$)* 13.2, 18.1, 20.0, 26.0, 26.1, 33.1, 36.1, 37.2, 43.1, 62.8, 124.9, 131.1, 131.8, 136.6, 171.0; *m/z* (EI$^+$) 253 (46, M^+), 238 (18, M^+-CH$_3^\cdot$), 193 (5, M^+-HOCH$_2$CH$_2$NH$^\cdot$), 170 (41, M^+-(CH$_3$)$_2$C=CHCH$_2$CH$_2^\cdot$), 109 (100%); (Found (ES$^+$) MH$^+$ 254.2112 $C_{15}H_{28}NO_2$ requires 254.2115).

***(E)*-3-[*(4S)*-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-(2-hydroxyethyl)-2-methyl-2-propenamide *(S,E)*-555**



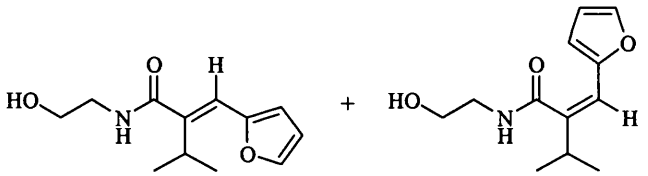
(S,E)-**555**

Reaction of aldolates **553** + **554** (0.100 g, 0.37 mmol) with a 0.5M solution of KHMDS (1.10 mL, 0.55 mmol) in THF (2 mL), according to general protocol K, gave the title

compound *(S,E)*-**555** in 80% d.e. The crude mixture was purified by silica gel chromatography (70% ethyl acetate/petrol) to afford the title compound *(S,E)*-**555** (0.035 g, 0.15 mmol) in 42% yield and >95% d.e. as a colourless oil, $[\alpha]_D^{25}$ +4.5 (c 1.54, CH_2Cl_2); ν_{max} *(neat)/cm*$^{-1}$ 3305 (br, OH, NH), 1668 $(C=O)_{am}$, 1622 (C=C), 1538 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.41 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.93 (3H, d, *J* 1.2, $CHC(CH_3)$), 3.27 (1H, s, O*H*), 3.47 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.61 (1H, app t, *J* 8.0, $CH_AH_BOCHOCH$=), 3.74 (2H, app t, *J* 5.0, CH_2OH), 4.15 (1H, dd, *J* 8.0, 6.0, $CH_AH_BOCHOCH$=), 4.84 (1H, app q, *J* 8.0, 6.5, $CH_2OCHOCH$=), 6.25 (1H, dq, *J* 8.0, 1.2, C*H*=C), 6.52 (1H, br s, N*H*); δ_C *($CDCl_3$)* 13.8, 26.2, 27.0, 43.0, 62.3, 69.2, 72.9, 110.1, 132.8, 135.1, 170.1; *m/z* (CI^+, *iso*-butane) 230 (98, MH^+), 214 (20, M^+ - $CH_3^{\cdot}$), 172 (68, M^+ - $(CH_3)_2CO$), 141 (63, M^+ - $HOCH_2CH_2NHCO$), 88 (100%); (Found (ES^+) MH^+ 230.1389 $C_{11}H_{20}NO_4$ requires 230.1387).

Reaction of *(S,E)*-amide **555** (0.020 g, 0.09 mmol) with a 0.5M solution of KHMDS (0.22 mL, 0.11 mmol) in THF (1 mL), according to general protocol K, afforded back the title compound *(S,E)*-**555** (0.014 g, 0.06 mmol) in > 95% d.e., $[\alpha]_D^{25}$ +4.8 (c 0.62, CH_2Cl_2).

_(E)_-3-(2-furyl)-_N_-(2-hydroxyethyl)-2-isopropyl-2-propenamide 558 and _(Z)_-3-(2-furyl)-_N_-(2-hydroxyethyl)-2-isopropyl-2-propenamide 559

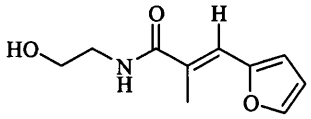


(E)-**558** + *(Z)*-**559**

Reaction of *syn*-3-{2-[2-furyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **557** (0.100 g, 0.37 mmol) with a 0.5M solution of KHMDS in toluene (1.12 mL, 0.56 mmol) in THF (2mL), according to general protocol K, gave the title compound *(E)*-**558** with 40% d.e. The crude product was partially purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound *(E)*-**558** (0.035 g, 0.16 mmol) in 42% yield and 60% d.e. as a yellow oil, ν_{max} *(neat)/cm*$^{-1}$ 3319 (br, OH, NH), 1644 (C=C), 1538 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 1.08 (6H, d, *J* 7.0, CH_3, *(Z)*-**559**), 1.18 (6H, d, *J* 7.0, CH_3, *(E)*-**558**), 2.74 (1H, br s, O*H*), 3.33 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.40 (2H, app. q, *J* 5.5, 4.5, CH_2NH), 3.68 (2H, app t, *J* 5.0, CH_2OH), 6.30 (2H, d, *J* 1.3, fur-*H*), 6.38 (1H, s, N*H*, *(Z)*-**559**), 6.52 (1H, s, N*H*, *(E)*-**558**), 6.45 (1H, s, *HC*=), 7.37 (1H, app t, *J* 1.3, fur-*H*); δ_C *($CDCl_3$)* 21.3 (2C), 29.1, 42.7, 62.7, 112.0, 112.5, 118.2, 142.4, 143.3, 151.4, 172.0;

m/z ($EI^{+\cdot}$) 223 (100, $M^{+\cdot}$), 163.0 (60%, $M^{+\cdot}$-$HOCH_2CH_2NH^{\cdot}$); (Found (ES^+) MH^+ 224.1281 $C_{12}H_{18}NO_3$ requires 224.1281).

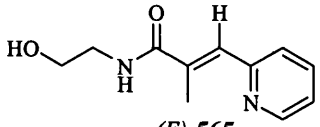
(*E*)-*N*-(2-hydroxyethyl)-2-methyl-3-(2-furyl)-2-propenamide 562



(*E*)-**562**

Reaction of *anti*-3-[3-(2-furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one **561** (0.200 g, 0.84 mmol) with a 0.5M solution of KHMDS in toluene (2.51 mL, 1.26 mmol) in THF (5 mL), according to general protocol K, afforded after silica gel chromatography (60% ethyl acetate/petrol) the title compound *(E)*-**562** (0.100 g, 0.51 mmol) in 61% yield and >95% d.e. as an orange oil, ν_{max} *(neat)/cm*$^{-1}$ 3376 (br, OH), 1646 $(C{=}O)_{am}$, 1609 (C=C), 1538 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 2.17 (3H, d, *J* 1.1, CH_3), 3.05 (1H, br s, O*H*), 3.47 (2H, app t, *J* 5.0, CH_2NH), 3.71 (2H, app t, *J* 5.0, CH_2OH), 6.39 (1H, dd, *J* 3.5, 1.8, fur-*H*), 6.40 (1H, br s, NH), 6.45 (1H, d, *J* 3.5, fur-*H*), 7.12 (1H, d, *J* 0.9, $CH{=}C(CH_3)$), 7.41 (1H. d, *J* 1.6, fur-*H*) ; δ_C *($CDCl_3$)* 14.7, 43.3, 62.8, 112.2, 114.4, 122.7, 127.8, 143.8, 152.3, 170.7; *m/z* ($EI^{+\cdot}$) 195 (43, $M^{+\cdot}$), 135 (100%, $M^{+\cdot}$-$HOCH_2CH_2NH^{\cdot}$); (Found (ES^+) MH^+ 196.0966 $C_{10}H_{14}NO_3$ requires 196.0968).

(*E*)-*N*-(2-hydroxyethyl)-2-methyl-3-(2-pyridinyl)-2-propenamide 565

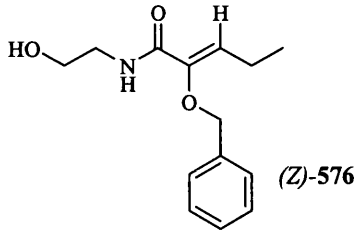


(*E*)-**565**

Reaction of *syn*-3-[3-hydroxy-2-methyl-3-(2-pyridinyl)propanoyl]-1,3-oxazolidin-2-one **564** (0.150 g, 0.60 mmol) with a 0.5M solution of KHMDS in toluene (1.80 mL, 0.90 mmol) in THF (3 mL), according to general protocol K, gave 0.109 g of an unpurified mixture of the title compound *(E)*-**565** (67%)in >95% d.e. and oxazolidinone **456** (33%) *via retro*-aldol pathway, as a brown oil, ν_{max} *(neat)/cm*$^{-1}$ 3318 (br, NH, OH), 3059 $(C\text{-}H)_{ar}$, 1732, 1651 $(C{=}O)_{am}$, 1621 (C=C), 1538 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 2.28 (3H, s, CH_3), 3.10 (1H, br s, OH), 3.52 (2H, app q, *J* 5.0, 5.0, CH_2N), 3.78 (2H, app t, *J* 5.0, CH_2OH), 7.02 (1H, br s, N*H*), 7.15-7.20 (1H, m, Pyr-*H*), 7.29 (1H, s, *H*C=), 7.32 (1H, d, *J* 7.5, Pyr-*H*), 7.67 (1H, app dt, J 7.5, 1.4, Pyr-*H*), 8.60 (1H, d, *J* 4.0, Pyr-*H*); δ_C *($CDCl_3$)* 14.7, 43.2, 62.1, 122.7, 125.8, 132.4, 136.2, 136.8, 149.6, 155.5, 171.0; *m/z* (CI^+, *iso*-

butane) 207 (44, MH^+), 189 (6, M^+-OH), 146 (45, M^+-$HO(CH_2)_2NH$), 118 (20, M^+-$CONH(CH_2)_2OH$), 88.0 (100%, oxazolidin-2-one+H^+).

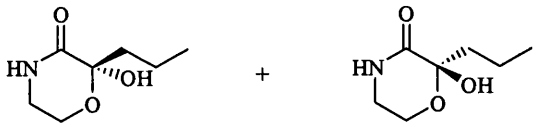
(*Z*)-2-(benzyloxy)-*N*-(2-hydroxyethyl)-2-pentenamide 576



(Z)-**576**

Reaction of *syn*-3-[2-(benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one **572** (0.200 g, 0.68 mmol) with a 0.5M solution of KHMDS in toluene (2.05 mL, 1.02 mmol) in THF (3 mL), according to general protocol K, gave a complex mixture of products which was purified by silica gel chromatography (gradient 60-100% ethyl acetate/petrol) to afford the title compound *(Z)*-**576** (0.030 g, 0.12 mmol) in 18% yield and > 95% d.e. as a pale-coloured oil, ν_{max} *(neat)/cm*$^{-1}$ 3419 (OH), 1649 $(C=O)_{am}$, 1634 (C=C), 1520 $(C=O)_{am}$, 1071 (C-O); δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.96 (3H, t, *J* 7.5, CH_2CH_3), 2.16 (2H, pentet, *J* 7.5, CH_2CH_3), 2.92 (1H, br s, O*H*), 3.32 (2H, app q, *J* 5.5, 5.0, CH_2OH), 3.57 (2H, app t, *J* 5.0, CH_2N), 4.70 (2H, s, CH_2Ph), 6.24 (1H, t, 7.5, *H*C=C), 6.76 (1H, br s, N*H*), 7.26-7.34 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 13.8, 19.7, 42.7, 62.8, 76.1, 127.3, 128.8, 129.0, 129.2, 136.9, 147.3, 165.5; *m/z* (CI^+, NH_3) 250 (100, MH^+), 160 (23%, M^+-CH_2Ph); (Found (ES^+) MH^+ 250.1436 $C_{14}H_{20}NO_3$ requires 250.1438).

(*2R*)-2-hydroxy-2-propyl-3-morpholinone 577 and (*2S*)-2-hydroxy-2-propyl-3-morpholinone 578

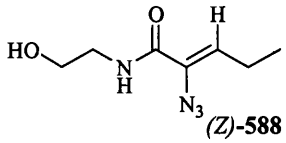


(R)-**577** + *(S)*-**578**

Reaction of *(Z)*-2-(benzyloxy)-*N*-(2-hydroxyethyl)-2-pentenamide **576** (0.020 g, 0.08 mmol) with Pd/C (0.005 g) under hydrogen for 12 hours in CH_2Cl_2 (1 mL) afforded after filtration over celite 0.010 g of an unpurified mixture of the title compound as a 1:1 mixture of isomers *(R)*-**577** and *(S)*-**578** (90%) and oxazolidin-2-one (10%), δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.89 (3H, t, *J* 7.5, $CH_2CH_2CH_3$), 0.88 (3H, t, *J* 7.5, $CH_2CH_2CH_3$), 1.58 (2H, sextet, *J* 7.5, $CH_2CH_2CH_3$), 1.39 (2H, sextet, *J* 7.5, $CH_2CH_2CH_3$), 2.84 (2H, app t, *J* 7.5, $CH_2CH_2CH_3$), 3.40 (2H, app dt, *J* 5.5, 5.0, CH_2NH), 3.70 (2H, app t, *J* 5.0, CH_2O), 6.97

(1H, br s, N*H*), 7.31 (1H, br s, N*H*); δ_C *(CDCl₃)* 14.0, 14.2, 17.1, 18.7, 37.2, 39.0, 40.9, 62.0, 62.7, 65.4; *m/z* (EI^+) 159.1 (12, $M^{+\cdot}$), 88.0 (100%, oxazolidin-2-one + H^+).

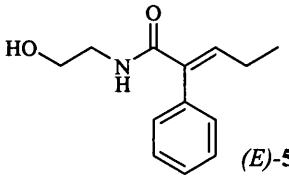
(*Z*)-2-azido-*N*-(2-hydroxyethyl)-2-pentenamide 588



(Z)-**588**

Reaction of *anti*-3-(2-azido-3-hydroxypentanoyl)-1,3-oxazolidin-2-one **587** (0.058 g, 0.26 mmol) with a 0.5M solution of KHMDS in toluene (0.77 mL, 0.38 mmol) in THF (1.5 mL), according to general protocol K, afforded 0.042 g of a mixture of the title compound (80%) in > 95% d.e. and oxazolidin-2-one (20%). The crude product was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound *(Z)*-**588** (0.017 g, 0.09 mmol) in 36% yield and >95% d.e. as a colourless oil, ν_{max} *(neat)/cm⁻¹* 3324 (br, OH, NH), 2117 (N=N=N), 1652 $(C=O)_{am}$, 1627 $(C=C)_{conj}$, 1538 $(C=O)_{am}$; δ_H *(300MHz, CDCl₃, Me₄Si)* 1.09 (3H, t, *J* 7.5, CH_2CH_3), 2.31 (2H, app quintet, *J* 7.5, CH_2CH_3), 2.85 (1H, br s, OH), 3.48 (2H, app dt, *J* 5.5, 4.5, CH_2NH), 3.77 (2H, app t, *J* 5.0, CH_2OH), 6.18 (1H, t, *J* 7.5, C*H*=C), 6.76 (1H, br s, N*H*); δ_C *(CDCl₃)* 13.7, 20.4, 42.9, 62.3, 129.9, 130.5, 164.0; *m/z* (CI^+, NH_3) 185 (30, MH^+), 159 (100), 157 (84%, M^+-OH); (Found (ES^+) MH^+ 185.1031 $C_7H_{13}N_4O_2$ requires 185.1033).

***(E)*-*N*-(2-hydroxyethyl)-2-phenyl-2-pentenamide 592**

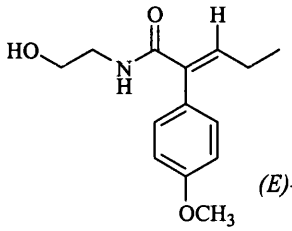


(E)-**592**

Reaction of s*yn*-3-(3-hydroxy-2-phenylpentanoyl)-1,3-oxazolidin-2-one **591** (0.200 g, 0.76 mmol) with a 0.5M solution of KHMDS in toluene (2.24 mL, 1.12 mmol) in THF (2 mL), according to general protocol K, gave a mixture (0.161 g) of the title compound *(E)*-**592** (70%) in > 95% d.e., the parent *N*-acyl oxazolidin-2-one **459** (15%) and an unknown product (15%). The crude product was purified by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound *(E)*-**592** (0.056 g, 0.26 mmol) in 34% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm⁻¹* 3418 (br, OH, NH), 1657 $(C=O)_{am}$, 1617 (C=C), 1522 $(C=O)_{am}$; δ_H *(300MHz, CDCl₃, Me₄Si)* 0.99 (3H, t, *J* 7.5, CH_2CH_3), 1.98 (2H, app pentet, *J* 7.5, CH_2CH_3), 3.16 (1H, br s, O*H*), 3.39 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.66

(2H, app t, *J* 5.0, C*H*$_2$OH), 5.79 (1H, br s, N*H*), 7.03 (1H, t, *J* 7.5, *H*C=C), 7.17-7.21 (2H, m, Ph-*H*), 7.35-7.46 (3H, m, Ph-*H*); δ_C *(CDCl$_3$)* 13.4, 23.1, 43.4, 62.8, 128.6, 129.0, 130.2, 135.1, 135.8, 143.8, 168.8; *m/z* (EI$^{+\cdot}$) 219 (18, $M^{+\cdot}$), 159 (22, $M^{+\cdot}$-HOCH$_2$CH$_2$NH$^{\cdot}$), 77 (100%); (Found (ES$^+$) *M*H$^+$ 220.1332 $C_{13}H_{18}NO_2$ requires 220.1332).

(*E*)-*N*-(2-hydroxyethyl)-2-(4-methoxyphenyl)-2-pentenamide 595

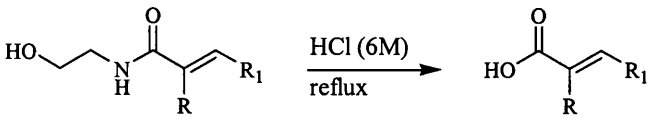


(E)-**595**

Reaction of s*yn*-3-[3-hydroxy-2-(4-methoxyphenyl)pentanoyl]-1,3-oxazolidin-2-one **594** (0.100 g, 0.34 mmol) with a 0.5M solution of KHMDS in toluene (1.02 mL, 0.51 mmol) in THF (2 mL), according to general protocol K, gave a mixture of the title compound *(E)*-**595** (80%) in 75% d.e. and the parent *N*-acyl oxazolidin-2-one **593** (20%). The crude product was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound *(E)*-**595** (0.033 g, 0.13 mmol) in 39% yield and >95% d.e. as a colourless oil, ν_{max} *(neat)/cm^{-1}* 3420 (br, OH, NH), 1653 (C=O)$_{am}$, 1617 (C=C), 1512 (C=O)$_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 0.91 (3H, t, *J* 7.5, CH$_2$C*H*$_3$), 1.92 (2H, app pentet, *J* 7.5, C*H*$_2$CH$_3$), 2.80 (1H, s, O*H*), 3.33 (2H, app q, *J* 5.5, 4.5, C*H*$_2$N), 3.59 (2H, app t, *J* 5.0, C*H*$_2$O), 3.77 (3H, s, ArOC*H*$_3$), 5.80 (1H, s, N*H*), 6.87 (2H, d, *J* 9.0, Ar-*H*), 6.93 (1H, t, *J* 7.5, *H*C=CAr), 7.04 (2H, d, *J* 9.0, Ar-*H*); δ_C *(CDCl$_3$)* 13.8, 23.1, 43.5, 55.7, 63.0, 114.7, 127.7, 131.4, 134.6, 143.7, 159.7, 169.2; *m/z* (EI$^{+\cdot}$) 249 (28, $M^{+\cdot}$), 161 (100%, $M^{+\cdot}$-HO(CH$_2$)$_2$)NHCO$^{\cdot}$; (Found (ES$^+$) *M*H$^+$ 250.1437 $C_{14}H_{20}NO_3$ requires 250.1438).

8-5 Preparation of carboxylic acids and oxazolines

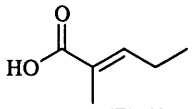
General protocol L



(E)-**631** *(E)*-**501**

(E)-α,β-Unsaturated amide **631** was refluxed for five hours in 6.0M HCl. Reaction mixture was allowed to cool to room temperature, saturated with sodium chloride, and extracted with ethyl acetate (5 x 10 ml). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo* to afford α,β-unsaturated carboxylic acid *(E)*-**501**.

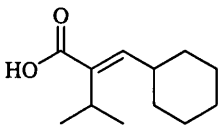
(*E*)-2-methylpenten-2-oic acid 495



(E)-**495**

The hydrolysis of (*E*)-*N*-(2-hydroxyethyl)-2-methyl-2-pentenamide **484** (0.300 g, 1.91 mmol) in 6.0M HCl (5 mL), according to general protocol L, afforded the title compound *(E)*-**495** (0.230 g, 2.02 mmol) in 91% yield and > 95% d.e. as a low-melting white solid, ν_{max} *(neat)/cm*$^{-1}$ 3429 (br, OH), 1700 (C=O), 1646 (C=C); δ_H *(300MHz, CDCl$_3$)* 0.99 (3H, t, *J* 7.5, CH_2CH_3), 1.76 (3H, d, *J* 0.9, $CH{=}CCH_3$), 2.14 (2H, app pentet, *J* 7.5, CH_2CH_3), 6.83 (1H, tq, 7.5, 1.4, $CH{=}CCH_3$), 10.5-11.8 (1H, br s, COOH); δ_C *(CDCl$_3$)* 12.2, 13.2, 22.6, 126.8, 147.2, 174.3.

(*E*)-3-cyclohexyl-2-isopropyl-2-propenoic acid 496[156]

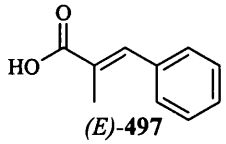


(E)-**496**

The hydrolysis of (*E*)-3-cyclohexyl-*N*-(2-hydroxyethyl)-2-isopropyl-2-propenamide **478** (0.053 g, 0.22 mmol) in 6.0M HCl (2 mL), according to general protocol L, afforded the title compound *(E)*-**496** (0.043 g, 0.22 mmol) in 99% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 1677 (C=O), 1621 $(C{=}C)_{conj}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 0.90-1.30 (6H, m, Cy-*H*), 1.13 (6H, d, *J* 7.0, $CH{=}CCH_3$), 1.52-1.72 (4H, m, Cy-*H*), 2.33 (1H, dtt, *J* 10.5, 10.0, 3.5, C*H*), 2.84 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 6.54 (1H, d, *J* 10.0, $CH{=}CCH_3$),

10.26 (1H, br s, COO*H*); δ_C *(CDCl₃)* 20.2, 24.5, 24.8, 26.4, 31.3, 31.9, 36.4, 134.1, 148.2, 172.7.; *m/z* ($EI^{+\cdot}$) 197.3 (15%, $MH^{+\cdot}$), 196.3 (15%, $M^{+\cdot}$); (Found ($EI^{+\cdot}$) $M^{+\cdot}$ 196.1454 $C_{12}H_{20}O_2$ requires 196.1458).

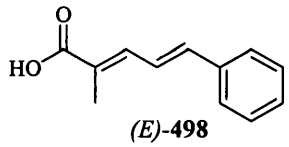
(*E*)-2-methyl-3-phenyl-2-propenoic acid 497



(E)-**497**

The hydrolysis of (*E*)-*N*-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide **486** (0.048 g, 0.23 mmol) in 6.0M HCl (3 mL), according to general protocol L, afforded the title compound *(E)*-**497** (0.036 g, 0.22 mmol) in 95% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm⁻¹* 3445 (br, OH), 1668 (C=O), 1616 $(C{=}C)_{conj}$, 1492 $(C{=}C)_{ar}$; δ_H *(300MHz, CDCl₃, Me₄Si)* 2.08 (s, 3H, CH=CC*H*₃), 7.26-7.36 (5H, m, Ph-*H*), 7.77 (1H, s, C*H*=CCH₃), 11.36 (1H, br s, COO*H*); δ_C *(CDCl₃)* 12.7, 126.5, 127.4, 127.7, 128.8, 134.5, 140.1, 173.4; *m/z* (EI^+) 162.1 (68%, $M^{+\cdot}$), 161.0 (36%, $M^{+\cdot}$-H·), 117.2 (58%, $M^{+\cdot}$-COOH·); (Found ($EI^{+\cdot}$) $M^{+\cdot}$ 162.0672 $C_{10}H_{10}O_2$ requires 162.0675).

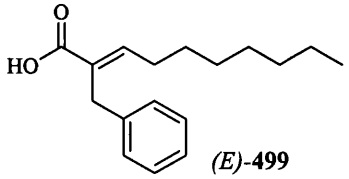
(2*E*,4*E*)-2-methyl-5-phenyl-2,4-pentadienoic acid 498[157]



(E)-**498**

The hydrolysis of (*E,E*)-*N*-(2-hydroxyethyl)-2-methyl-5-phenyl-2,4-pentadienamide **493** (0.200 g, 0.58 mmol) in 6.0M HCl (5 mL), according to general protocol L, afforded the title compound *(E,E)*-**498** (0.135 g, 0.45 mmol) in 77% yield and > 95% d.e. as a pale brown solid, *mp* 158-160°C (lit,[157] 160.0-162.5°C); ν_{max} *(KBr disc)/cm⁻¹* 3445 (br, OH), 1683 (C=O), 1622 $(C{=}C)_{conj}$, 1495 $(C{=}C)_{ar}$; δ_H *(300MHz, CDCl₃, Me₄Si)* 1.98 (3H, d, *J* 1.1, CH_3), 6.83 (1H, d, *J* 15.5, C*H*CH=CHPh), 7.00 (1H, dd, *J* 15.5, 11.5, CHC*H*=CHPh), 7.17-7.45 (6H, m, CHCH=C*H*Ph, Ph-*H*), 10.00-12.00 (1H, br s, COO*H*); δ_C *(CDCl₃)* 11.5, 122.7, 125.4, 126.2, 127.8, 127.9, 135.4, 139.2, 139.6, 173.0; *m/z* ($EI^{+\cdot}$) 188 (33, $M^{+\cdot}$), 143 (62, $M^{+\cdot}$-COOH·), 128 (80, $M^{+\cdot}$-COOH-CH_3), 115 (100%, $M^{+\cdot}$-C(CH_3)COOH-H^+); (Found ($ES^{+\cdot}$) MNH_4^+ 206.1175 $C_{12}H_{16}NO_2$ requires 206.1176).

(*E*)-2-benzyl-2-decenoic acid 499

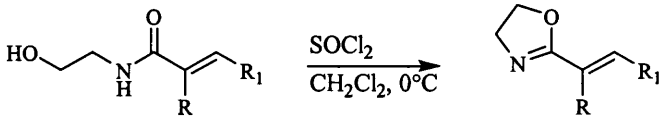


(E)-**499**

The hydrolysis of (*E*)-2-benzyl-*N*-(2-hydroxyethyl)-2-decenamide **489** (0.200 g, 0.58 mmol) in 6.0M HCl (5 mL), according to general protocol L, afforded the title compound *(E)*-**499** (0.135 mg, 0.45 mmol) in 77% yield and > 95% d.e., δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.80 (3H, t, *J* 7.0, CH_3), 1.12-1.25 (8H, m, Alk-*H*), 1.29-1.38 (2H, m, CH_2CH_2CH=C), 2.19 (2H, app q, *J* 7.5, CH_2CH_2CH=C), 3.58 (2H, s, CH_2Ph), 6.97-7.17 (5H, m, Ph-*H*); δ_C *($CDCl_3$)* 13.0, 21.6, 27.5, 28.0, 28.2, 28.3, 30.7, 31.2, 125.0, 127.2, 127.3, 129.2, 138.5, 146.1, 171.9; *m/z* ($EI^{+\cdot}$) 260.3 (66, $M^{+\cdot}$), 242 (9, $M^{+\cdot}$-H_2O), 161 (14, $M^{+\cdot}$- $CH_3(CH_2)_6^{\cdot}$), 91 (100%); (Found (EI^+) M^+ 278.2118 $C_{17}H_{28}NO_2$ requires 278.2120).

Preparation of oxazolines

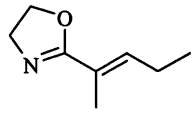
General protocol M



(E)-**631** *(E)*-**500**

Thionyl chloride (5 eq.) was added dropwise to a stirred solution of α,β-unsaturated amide *(E)*-**631** (1 eq.) in CH_2Cl_2 in an ice bath. Reaction mixture was stirred for 2 hours at this temperature. A 5.0M solution of NaOH (3 mL) was added dropwise and the reaction extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford oxazoline *(E)*-**500**

2-[(*E*)-1-methyl-1-butenyl]-4,5-dihydro-1,3-oxazole 505

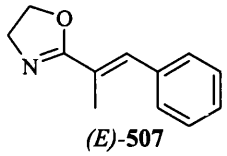


(E)-**505**

Reaction of (*E*)-*N*-(2-hydroxyethyl)-2-methyl-2-pentenamide **484** (0.112 g, 0.71 mmol) with thionyl chloride (0.26 mL, 3.57 mmol) in CH_2Cl_2 (4 mL), according to general protocol M, gave the title compound *(E)*-**505** (0.087 g, 0.63 mmol) in 88% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm^{-1}* 1700 (C=N), 1653 (C=C); δ_H *(300MHz, $CDCl_3$)* 0.97 (3H, t, *J* 7.6, CH_2CH_3), 1.85 (3H, s, CH=CCH_3), 2.12 (2H, app pentet, *J* 7.5,

CH_2CH_3), 3.86 (2H, t, *J* 9.5, CH_2), 4.20 (2H, t, *J* 9.5, CH_2), 6.34 (1H, t, *J* 7.4, CH=CCH_3); δ_C *(CDCl3)* 13.5, 13.7, 22.1, 55.1, 67.5, 123.9, 140.1, 166.8; *m/z* ($EI^{+\cdot}$) 139 (55%, $M^{+\cdot}$), 124 (100%, $M^{+\cdot}$-$CH_3^{\cdot}$); (Found (ES^+) MH^+ 140.1072 $C_8H_{14}NO$ requires 140.1070).

2-[*(E)*-1-methyl-2-phenyl-1-ethenyl]-4,5-dihydro-1,3-oxazole 507



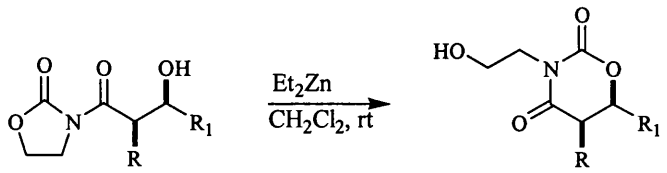
(E)-**507**

Reaction of *(E)-N*-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide **486** (0.570 g, 2.78 mmol) with thionyl chloride (0.89 mL, 12.20 mmol) in CH_2Cl_2 (15 mL), according to general protocol M, gave the title compound *(E)*-**507** (0.503 g, 2.69 mmol) in 97% yield and > 95% d.e. as a pale yellow oil, ν_{max} *(neat)/cm*$^{-1}$ 1707 (C=N), 1640 (C=C), 1614 $(C=C)_{ar}$, 1491 $(C=C)_{ar}$; δ_H *(300MHz, CDCl3, Me4Si)* 2.21 (3H, d, *J* 1.5, CH=CCH_3), 4.01 (2H, app t, *J* 9.5, CH_2N), 4.36 (2H, app t, *J* 9.5, CH_2O), 7.35-7.40 (5H, m, Ph-*H*); δ_C *(CDCl3)* 15.4, 55.4, 67.9, 125.7, 128.2, 128.7, 129.9, 135.6, 136.7, 167.3; *m/z* ($EI^{+\cdot}$) 187 (27, $M^{+\cdot}$), 186 (100, $M^{+\cdot}$-$H^{\cdot}$), 129 (7, $M^{+\cdot}$-OCH_2CH_2N), 115 (25%, CH_3CCPh^+); (Found (EI^+) M^+ 187.0998 $C_{12}H_{13}NO$ requires 187.0997).

8.6 Preparation of oxazinanediones

Procedure for the rearrangement reaction with diethylzinc

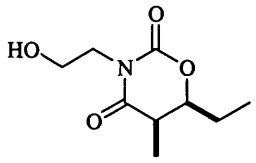
General protocol N



syn-**627** *syn*-**632**

A 1.0M solution of Et_2Zn in toluene (0.1 eq.) was added dropwise to a stirred solution of *syn*-aldolate **627** (1 eq.) in CH_2Cl_2 at room temperature. The reaction was stirred for 2 hours. Saturated NH_4Cl_{aq} was added and the reaction extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford *syn*-oxazinanedione **632**.

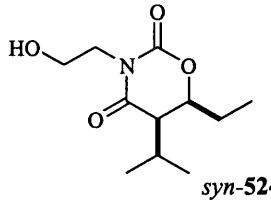
syn-6-Ethyl-3-(2-hydroxyethyl)-5-methyl-1,3-oxazinane-2,4-dione 522



syn-**522**

Reaction of *syn*-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one **479** (0.050 g, 0.25 mmol) with a 1.0M solution of Et_2Zn in toluene (0.03 mL, 0.03 mmol) in CH_2Cl_2 (2 mL), according to general protocol N, afforded the title compound **522** (0.029 g, 0.14 mmol) in 58% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3433 (br, OH), 1750 $(C{=}O)_{ox}$, 1695 $(C{=}O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.98 (3H, t, *J* 7.5, CH_2CH_3), 1.17 (3H, d, *J* 7.0, $CHCH_3$), 1.55 (1H, dqd, *J* 14.0, 7.5, 5.0, $CH_AH_BCH_3$), 1.71 (1H, dqd, *J* 14.0, 9.0, 7.5, $CH_AH_BCH_3$), 1.92 (1H, br s, O*H*), 2.79 (1H, qd, *J* 7.0, 3.5, $CHCH_3$), 3.74 (2H, app t, *J* 5.0, CH_2OH), 3.91 (1H, ddd, *J* 14.0, 5.5, 5.0, CH_AH_BN), 3.99 (1H, app dt, *J* 14.0, 5.5, CH_AH_BN), 4.34 (1H, ddd, *J* 9.0, 5.0, 3.5, $CHCH_2CH_3$); δ_C *($CDCl_3$)* 8.6, 8.6, 22.0, 38.0, 48.1, 60.0, 77.7, 151.2, 171.9; *m/z* (CI^+, *iso*-butane) 202 (87, MH^+), 158 (60%, MH^+-CO_2); (Found (FAB^+) MH^+ 202.1080 $C_9H_{16}NO_4$ requires 202.1079).

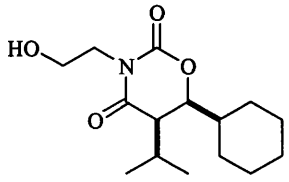
syn-6-Ethyl-3-(2-hydroxyethyl)-5-isopropyl-1,3-oxazinane-2,4-dione 524



syn-**524**

Reaction of *syn*-3-(3-hydroxy-2-isopropylpentanoyl)-1,3-oxazolidin-2-one **480** (0.250 g, 1.09 mmol) with a 1.0M solution of Et_2Zn in toluene (0.11 mL, 0.11 mmol) in CH_2Cl_2 (5 mL), according to general protocol N, afforded the title compound *syn*-**524** (0.220 g, 0.96 mmol) in 88% yield and > 95% d.e. as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3436 (br, OH), 1749 $(C=O)_{ox}$, 1691 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.97 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.00 (3H, t, *J* 7.5, CH_2CH_3), 1.02 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.60 (1H, dqd, *J* 14.0, 7.5, 5.0, $CH_AH_BCH_3$), 1.80 (1H, dqd, *J* 14.0, 9.0, 7.5, $CH_AH_BCH_3$), 2.08-2.21 (1H, septet of d, *J* 7.0, 5.0, $CH(CH_3)_2$), 2.25 (1H, br s, O*H*), 2.52 (1H, dd, *J* 5.0, 4.0, C*H*^{i}Pr), 3.74 (2H, app t, *J* 5.5, CH_2OH), 3.89 (1H, app dt, *J* 14.0, 5.5, CH_AH_BN), 4.01 (1H, app dt, *J* 14.0, 5.5, CH_AH_BN), 4.39 (1H, ddd, *J* 9.0, 5.0, 4.0, C*H*Et); δ_C *($CDCl_3$)* 9.0, 18.8, 21.2, 22.3, 14.5, 43.1, 48.4, 59.8, 78.0, 151.6, 170.0; *m/z* (CI^+, NH_3) 247 (94, MH^+), 230 (100, MH^+), 186 (31%, MH^+-CO_2); (Found (ES^+) MH^+ 230.1387 $C_{11}H_{20}NO_4$ requires 230.1387).

syn-6-Cyclohexyl-3-(2-hydroxyethyl)-5-isopropyl-1,3-oxazinane-2,4-dione 525

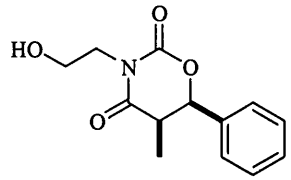


syn-**525**

Reaction of *syn*-3-{2-[cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **476** (0.070 g, 0.25 mmol) with a 1.0M solution of Et_2Zn in toluene (0.03 mL, 0.03 mmol) in CH_2Cl_2 (2 mL), according to general protocol N, afforded the title compound *syn*-**525** (0.064 g, 0.22 mmol) in 90% yield and > 95% d.e. as a white solid, *mp* 100-102°C ; ν_{max} *(KBr disc)/cm*$^{-1}$ 3408 (br, OH), 1757 $(C=O)_{ox}$, 1696 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.93 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.06 (3H, d, *J* 7.0, $CH(CH_3)_2$), 0.82-1.30 (6H, m, Cy-*H*), 1.48-1.78 (4H, m, Cy-*H*), 2.07 (1H, t, *J* , O*H*), 2.14-2.24 (2H, m, $CH(CH_3)_2$, Cy-*H*), 2.59 (1H, app t, *J* 3.0, C*H*^{i}Pr), 3.73-3.79 (2H, m, CH_2OH), 3.82-3.90 (1H, m, C*H*Cy), 4.02-4.10 (2H, m, CH_2N); δ_C *($CDCl_3$)* 17.8, 22.0, 24.1, 24.4, 24.6, 25.0,

26.8, 28.5, 36.4, 43.2, 46.4, 60.1, 80.7, 151.9, 170.0; *m/z* (CI^+, *iso*-butane) 284 (65, MH^+), 240 (100%, MH^+-CO_2); (Found (FAB^+) MH^+ 284.1855 $C_{15}H_{26}NO_4$ requires 284.1862).

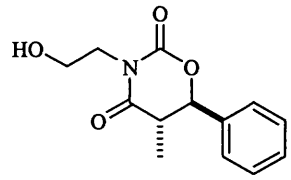
syn-3-(2-Hydroxyethyl)-5-isopropyl-6-phenyl-1,3-oxazinane-2,4-dione 517



syn-**517**

Reaction of *syn*-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one **467** (0.150 g, 0.60 mmol) with a 1.0M solution of Et_2Zn in toluene (0.06 mL, 0.06 mmol) in CH_2Cl_2 (3 mL), according to general protocol N, afforded the title compound *syn*-**517** (0.147 g, 0.58 mmol) in 97% yield and 90% d.e. as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3447 (br, OH), 1755 $(C=O)_{ox}$, 1703 $(C=O)_{am}$, 1500 $(C=C)_{ar}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 1.01 (3H, d, *J* 7.5, C*H*$_3$), 2.17 (1H, s, O*H*), 2.99 (1H, qd, *J* 7.5, 3.5, C*H*CH$_3$), 3.75-3.82 (2H, m, C*H*$_2$OH), 3.97 (1H, app dt, *J* 14.0, 5.5, C*H*$_A$H$_B$N), 4.05 (1H, app dt, *J* 14.0, 5.5, CH$_A$*H*$_B$N), 5.62 (1H, d, *J* 3.5, C*H*Ph), 7.24–7.38 (5H, m, Ph-*H*); δ_C *(CDCl$_3$)* 10.4, 41.5, 44.6, 61.2, 78.1, 126.0, 129.2, 129.4, 134.4, 152.4, 173.2; *m/z* (CI^+, NH_3) 267 (15, MNH_4^+), 206 (47, MH^+-CO_2), 105 (100%); (Found (ES^+) MH^+ 250.1081 $C_{13}H_{16}NO_4$ requires 250.1079).

anti-3-(2-Hydroxyethyl)-5-isopropyl-6-phenyl-1,3-oxazinane-2,4-dione 518

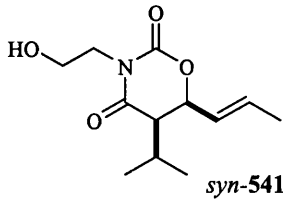


anti-**518**

Reaction of *anti*-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one **468** (0.050 g, 0.20 mmol) with a 1.0M solution of Et_2Zn in toluene (0.02 mL, 0.02 mmol) in CH_2Cl_2 (1 mL), according to general protocol N, afforded the title compound *anti*-**518** (0.047 g, 0.19 mmol) in 96% yield and > 95% d.e. as a white solid, ν_{max} *(neat)/cm*$^{-1}$ 3435 (br, OH), 1755 $(C=O)_{ox}$, 1694 $(C=O)_{am}$, 1501 $(C=C)_{ar}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 1.02 (3H, d, *J* 7.0, C*H*$_3$), 2.21 (1H, br s, O*H*), 2.89 (1H, qd, *J* 11.5, 7.0, C*H*(CH$_3$)), 3.77-3.80 (2H, app t, *J* 5.5 , C*H*$_2$OH), 3.94 (1H, ddd, *J* 14.0, 6.0, 4.5, C*H*$_A$H$_B$N), 4.06 (1H, app dt, *J* 14.0, 5.5, CH$_A$*H*$_B$N), 5.04 (1H, d, *J* 11.5, C*H*Ph), 7.24-7.38 (5H, m, Ph-*H*); δ_C *(CDCl$_3$)* 10.1, 40.4, 43.5, 59.6, 80.5, 126.1, 127.9, 128.7, 134.2, 151.1, 170.5; *m/z* (CI^+, NH_3) 267

(MNH_4^+, 100%), 250 (46, MH^+), 208 (55), 206 (87%, MH^+-CO_2); (Found (ES^+) MH^+ 250.1077 $C_{13}H_{16}NO_4$ requires 250.1079).

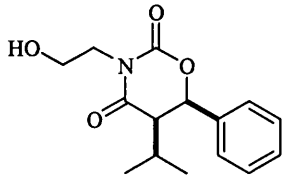
syn-3-(2-Hydroxyethyl)-5-isopropyl-6-[(*E*)-1-propenyl]-1,3-oxazinane-2,4-dione 541



syn-**541**

Reaction of *syn*-3-[*(E)*-3-hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one **463** (0.200 g, 0.83 mmol) with a 1.0M solution of Et_2Zn in toluene (0.08 mL, 0.08 mmol) in CH_2Cl_2 (5 mL), according to general protocol O, afforded the title compound *syn*-**541** (0.129 g, 0.54 mmol) in 65% yield and > 95% d.e as a colourless oil, ν_{max} *(neat)/cm*$^{-1}$ 3430 (br, OH), 1755 $(C=O)_{ox}$, 1699 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.97 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.03 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.71 (3H, d, *J* 7.0, $CH_3CH=CH$), 1.97 (1H, t, *J* 5.5, O*H*), 2.10 (1H, app octet, *J* 7.0, $CH(CH_3)_2$), 2.55 (1H, dd, *J* 6.5, 4.5, CH^iPr), 3.74 (2H, app dt, *J* 5.5, 5.5, CH_2OH), 3.94-3.98 (2H, m, CH_2N), 4.92 (1H, app t, *J* 6.5, $CHCH=CHCH_3$), 5.47 (1H, ddd, *J* 15.0, 7.0, 1.5, $CH_3CH=CH$), 5.91 (1H, dq, *J* 15.0, 7.0, $CH_3CH=CH$) ; δ_C *($CDCl_3$)* 17.0, 19.7, 20.3, 24.8, 43.2, 49.5, 60.1, 76.6, 122.1, 132.7, 151.3, 169.7; *m/z* ($EI^{+\cdot}$) 241 (41, $M^{+\cdot}$), 198 (100%, $M^{+\cdot}$-CO_2); (Found ($EI^{+\cdot}$) M^+ 241.1313 $C_{12}H_{19}NO_4$ requires 241.1314).

syn-3-(2-Hydroxyethyl)-5-isopropyl-6-phenyl-1,3-oxazinane-2,4-dione 608

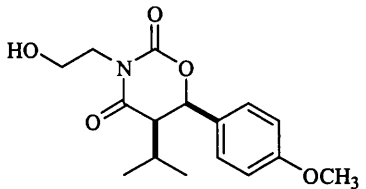


syn-**608**

Reaction of *syn*-3-{2-[hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **481** (0.300 g, 1.08 mmol) with a 1.0M solution of Et_2Zn in toluene (0.11 mL, 0.11 mmol) in CH_2Cl_2 (5 mL), according to general protocol O, gave the title compound *syn*-**608** in 80% d.e. The crude product was purified by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound *syn*-**608** (0.155 g, 0.56 mmol) in 52% yield and > 95% d.e. as a white solid, *mp* 92-94°C*;* ν_{max} *(KBr disc)/cm*$^{-1}$ 3447 (br, OH), 1734 $(C=O)_{ox}$, 1684 $(C=O)_{am}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.85 (3H, d, *J* 7.0, $CH(CH_3)_2$), 0.94

(3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.88-1.90 (1H, septet of d, *J* 7.0, 4.0, C*H*(CH$_3$)$_2$), 2.76 (1H, br s, O*H*), 2.85 (1H, app t, *J* 4.0, C*H*^{i}Pr), 3.85 (2H, app t, *J* 5.0, C*H*$_2$OH), 4.01 (1H, app dt, *J* 14.0, 5.0, C*H*$_A$H$_B$N), 4.12 (1H, app dt, *J* 14.0, 5.0, CH$_A$*H*$_B$N), 5.79 (1H, d, *J* 4.0, C*H*Ph), 7.33-7.43 (5H, m, Ph-*H*); δ_C *(CDCl$_3$)* 21.0, 24.6, 27.4, 46.0, 53.3, 62.3, 79.8, 127.0, 130.3, 130.7, 136.4, 154.1, 172.6; *m/z* (CI$^+$, NH$_3$) 295 (85, *M*NH$_4^+$), 278 (52, *M*H$^+$), 234 (44, *M*H$^+$-CO$_2$), 189.2 (100%); (Found (ES$^+$) *M*H$^+$ 278.1385 $C_{15}H_{20}NO_4$ requires 278.1387).

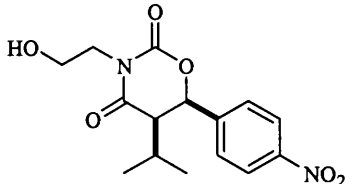
syn-3-(2-Hydroxyethyl)-5-isopropyl-6-(4-methoxyphenyl-1,3-oxazinane-2,4-dione 610



syn-**610**

Reaction of *syn*-3-{2-[hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **482** (0.100 g, 0.33 mmol) with a 1.0M solution of Et_2Zn in toluene (0.03 mL, 0.03 mmol) in CH_2Cl_2 (3 mL), according to general protocol O, gave the title compound *syn*-**610** in 80% d.e. The crude product was purified by silica gel chromatography (20% ethyl acetate/petrol) to afford the title compound *syn*-**610** (0.061 g, 0.20 mmol) in 61% yield and > 95% d.e. as a white solid, *mp* 79-81°C; ν_{max} *(KBr disc)/cm*$^{-1}$ 3353 (br, OH), 1740 (C=O)$_{ox}$, 1691 (C=O)$_{am}$; δ_H *(300MHz, CDCl$_3$, Me$_4$Si)* 0.87 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 0.98 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.96 (1H, septet of d, *J* 7.0, 4.0, C*H*(CH$_3$)$_2$), 2.16-2.26 (1H, m, C*H*^{i}Pr), 2.79 (1H, t, *J* 4.0, O*H*)), 3.83 (3H, s, ArOC*H*$_3$), 3.81-3.87 (2H, m, C*H*$_2$OH), 4.02 (1H, app dt, *J* 14.0, 5.5, C*H*$_A$H$_B$N), 4.16 (1H, app dt, *J* 14.0, 5.5, CH$_A$*H*$_B$N), 5.71 (1H, d, *J* 4.0, C*H*Ar), 6.94 (2H, d, *J* 8.5, Ar-*H*), 7.29 (2H, d, *J* 8.5, Ar-*H*); δ_C *(CDCl$_3$)* 19.8, 23.1, 26.0, 44.7, 52.0, 55.7, 61.3, 78.4, 114.6, 126.7, 127.1, 152.9, 160.1, 171.4; *m/z* (EI$^{+\cdot}$) 307 (29, *M*$^{+\cdot}$), 263 (4, *M*$^{+\cdot}$-CO$_2^{\cdot}$), 84 (100%); (Found (EI$^{+\cdot}$) *M*$^{+\cdot}$ 307.1419 $C_{16}H_{21}NO_5$ requires 307.1420).

syn-3-(2-Hydroxyethyl)-5-isopropyl-6-(4-nitrophenyl)-1,3-oxazinane-2,4-dione 613



syn-**613**

Reaction of *syn*-3-{2-[hydroxy(4-nitrophenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **613** (0.250 g, 0.78 mmol) with a 1.0M solution of Et_2Zn in toluene (0.08 mL, 0.08 mmol) in CH_2Cl_2 (4 mL), according to general protocol O, gave the title compound *syn*-**614** in 70% d.e. The crude product was purified by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound *syn*-**614** (0.126 g, 0.39 mmol) in 51% yield in >95% d.e. as a yellow solid, *mp* 149-151°C ν_{max} *(neat)/cm*$^{-1}$ 3513 (br, OH), 1762 $(C=O)_{ox}$, 1700 $(C=O)_{am}$, 1600 $(C=C)_{ar}$, 1522 $(N=O)_{conj}$, 1347 $(N=O)_{conj}$; δ_H *(300MHz, $CDCl_3$, Me_4Si)* 0.89 (3H, d, *J* 7.0, $CH(CH_3)_2$), 0.96 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.81 (1H, septet of d, *J* 7.0, 3.5, $CH(CH_3)_2$), 2.16 (1H, br s, O*H*), 2.94 (1H, app t, *J* 3.5, C*H*^{i}Pr), 3.88 (2H, app t, *J* 5.0, CH_2OH), 4.04 (1H, ddd, *J* 14.0, 6.5, 4.5, CH_AH_BN), 4.18 (1H, app dt, *J* 14.0, 5.0, CH_AH_BN), 5.89 (1H, d, *J* 3.5, C*H*Ar), 7.62 (2H, d, *J* 8.5, Ar-*H*), 8.30-8.35 (2H, m, *J* 8.5, Ar-*H*); δ_C *($CDCl_3$)* 19.4, 23.3, 26.3, 44.7, 51.6, 60.9, 77.5, 124.6, 126.6, 142.1, 148.3, 152.0, 170.2; *m/z* (CI^+, *iso*-butane) 323 (80, MH^+), 279 (87, MH^+-CO_2), 88 (100%); (Found (FAB^+) MH^+ 323.1244 $C_{15}H_{19}N_2O_6$ requires 323.1243).

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Appendix 1. X-Ray crystallographic Data for (*E*)-3-cyclohexyl-*N*-(2-hydroxyethyl)-2-isopropyl-2-propenamide 478

k02sdb1

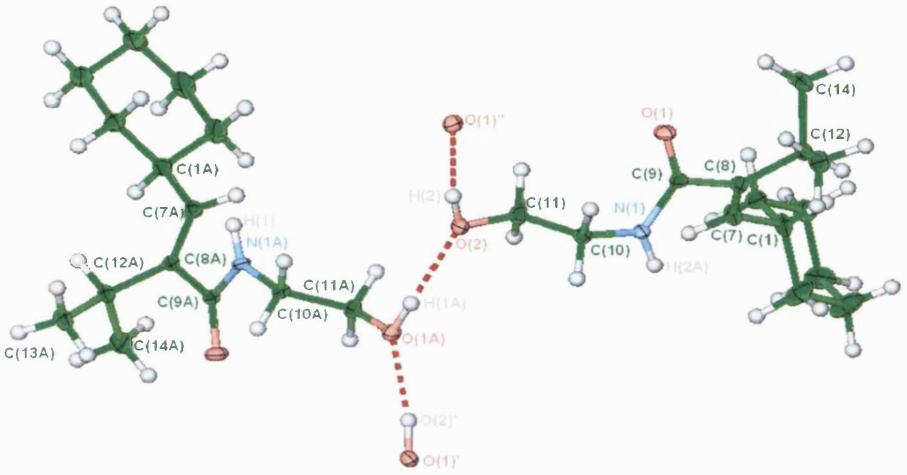

Table 1. Crystal data and structure refinement for *(E)*-**478**.

Identification code	k02sdb1
Empirical formula	$C_{14}H_{25}NO_2$
Formula weight	239.35
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 17.3540(2) $\alpha = 90^\circ$ b = 9.79700(10)Å $\beta = 104.1530(10)^\circ$ c = 17.7370(2)Å $\gamma = 90^\circ$
Volume	2924.06(6) $Å^3$
Z	8
Density (calculated)	1.087 Mg/m^3
Absorption coefficient	0.071 mm^{-1}
F(000)	1056
Crystal size	0.50 x 0.30 x 0.10 mm
Theta range for data collection	2.94 to 27.46°
Index ranges	-22<=h<=22; -11<=k<=12; -22<=l<=23
Reflections collected	43295
Independent reflections	6676 [R(int) = 0.0787]
Reflections observed (>2□)	4436
Data Completeness	0.998
Max. and min. transmission	0.9929 and 0.9651
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6676 / 0 / 368
Goodness-of-fit on F^2	1.007
Final R indices [I>2□(I)]	$R_1 = 0.0453$, $wR_2 = 0.1035$
R indices (all data)	$R_1 = 0.0818$, $wR_2 = 0.1198$
Largest diff. peak and hole	0.232 and -0.215 $eÅ^{-3}$

Notes: Disorder modelled for cyclohexyl ring based on C1A. Atoms C2A–C6A disordered in 55:45 ratio with C2C–C6C respectively. Extensive H–bonding is present lattice based on the following contacts.

Hydrogen bonds with H..A < r(A) + 2.000 Å and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O2-H2	0.840	1.948	170.62	2.780	O1A [-x+1, y+1/2, -z+1/2]
O1A-H1A	0.840	1.969	165.13	2.789	02
N1A-H1	0.849	1.968	164.15	2.794	O1 [x, -y+1/2, z+1/2]
N1-H2A	0.861	1.951	164.80	2.791	O2A [x, -y-1/2, z-1/2]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for *(E)*-**478**.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3704(1)	2365(1)	-431(1)	39(1)
O(2)	4688(1)	907(1)	2057(1)	34(1)
O(1A)	4739(1)	-1445(1)	2954(1)	34(1)
O(2A)	3628(1)	-2354(1)	4869(1)	39(1)
N(1)	3835(1)	179(1)	-35(1)	29(1)
N(1A)	3789(1)	-208(1)	4491(1)	28(1)
C(1)	1708(1)	-882(2)	-1777(1)	39(1)
C(2)	1846(1)	-2408(2)	-1863(1)	61(1)
C(3)	1144(1)	-3085(2)	-2433(1)	77(1)
C(4)	374(1)	-2825(2)	-2216(1)	62(1)
C(5)	231(1)	-1328(2)	-2139(1)	46(1)
C(6)	921(1)	-680(2)	-1556(1)	42(1)
C(7)	2377(1)	-270(2)	-1171(1)	37(1)
C(8)	2895(1)	691(1)	-1248(1)	30(1)
C(9)	3509(1)	1156(1)	-538(1)	28(1)
C(10)	4444(1)	458(1)	674(1)	30(1)
C(11)	4090(1)	816(2)	1347(1)	35(1)
C(12)	2898(1)	1387(1)	-2014(1)	32(1)
C(13)	3737(1)	1567(2)	-2123(1)	44(1)
C(14)	2454(1)	2743(2)	-2113(1)	51(1)
C(1A)	1636(1)	1006(2)	5132(1)	36(1)
C(2A)	976(4)	1444(6)	4444(4)	49(1)
C(3A)	311(4)	2192(8)	4716(4)	58(2)
C(4A)	630(5)	3416(9)	5224(4)	59(2)
C(5A)	1305(5)	2979(10)	5907(4)	51(1)
C(6A)	1957(5)	2243(9)	5631(3)	42(1)
C(7A)	2304(1)	341(1)	4866(1)	33(1)
C(8A)	2801(1)	-626(1)	5217(1)	29(1)
C(9A)	3437(1)	-1135(1)	4846(1)	27(1)
C(10A)	4423(1)	-554(1)	4116(1)	29(1)
C(11A)	4106(1)	-1183(2)	3320(1)	32(1)
C(12A)	2758(1)	-1291(1)	5982(1)	34(1)
C(13A)	3579(1)	-1431(2)	6539(1)	50(1)
C(14A)	2323(1)	-2664(2)	5856(1)	49(1)
C(2C)	845(5)	899(7)	4495(5)	50(2)
C(3C)	151(5)	1577(8)	4738(6)	60(2)
C(4C)	360(7)	3047(10)	4975(7)	64(3)
C(5C)	1090(5)	3164(10)	5595(6)	75(3)
C(6C)	1805(6)	2485(11)	5348(5)	67(2)

Table 3. Bond lengths [Å] and angles [°] for *(E)*-**478**.

O(1)-C(9)	1.2338(15)	O(2)-C(11)	1.4260(16)
O(1A)-C(11A)	1.4302(15)	O(2A)-C(9A)	1.2374(15)
N(1)-C(9)	1.3370(17)	N(1)-C(10)	1.4558(17)
N(1A)-C(9A)	1.3356(17)	N(1A)-C(10A)	1.4571(16)
C(1)-C(7)	1.501(2)	C(1)-C(6)	1.522(2)
C(1)-C(2)	1.528(2)	C(2)-C(3)	1.530(2)
C(3)-C(4)	1.501(3)	C(4)-C(5)	1.499(2)
C(5)-C(6)	1.517(2)	C(7)-C(8)	1.3310(19)
C(8)-C(9)	1.5071(19)	C(8)-C(12)	1.5216(18)
C(10)-C(11)	1.5130(19)	C(12)-C(13)	1.524(2)
C(12)-C(14)	1.525(2)	C(1A)-C(6C)	1.509(11)
C(1A)-C(7A)	1.5032(19)	C(1A)-C(2A)	1.517(7)
C(1A)-C(6A)	1.524(9)	C(1A)-C(2C)	1.553(10)
C(2A)-C(3A)	1.541(10)	C(3A)-C(4A)	1.521(9)
C(4A)-C(5A)	1.526(7)	C(5A)-C(6A)	1.520(12)
C(7A)-C(8A)	1.3297(19)	C(8A)-C(9A)	1.5032(18)
C(8A)-C(12A)	1.5218(18)	C(10A)-C(11A)	1.5159(18)
C(12A)-C(13A)	1.528(2)	C(12A)-C(14A)	1.532(2)
C(2C)-C(3C)	1.527(13)	C(3C)-C(4C)	1.519(10)
C(4C)-C(5C)	1.464(11)	C(5C)-C(6C)	1.561(13)
C(9)-N(1)-C(10)	122.81(12)	C(9A)-N(1A)-C(10A)	122.70(11)
C(7)-C(1)-C(6)	110.46(12)	C(7)-C(1)-C(2)	110.45(13)
C(6)-C(1)-C(2)	108.99(13)	C(1)-C(2)-C(3)	111.78(15)
C(4)-C(3)-C(2)	111.82(16)	C(5)-C(4)-C(3)	111.57(16)
C(4)-C(5)-C(6)	110.55(14)	C(5)-C(6)-C(1)	112.27(12)
C(8)-C(7)-C(1)	129.24(13)	C(7)-C(8)-C(9)	119.02(12)
C(7)-C(8)-C(12)	123.95(13)	C(9)-C(8)-C(12)	117.01(11)
O(1)-C(9)-N(1)	121.90(13)	O(1)-C(9)-C(8)	122.07(12)
N(1)-C(9)-C(8)	116.03(11)	N(1)-C(10)-C(11)	112.06(11)
O(2)-C(11)-C(10)	111.29(11)	C(8)-C(12)-C(13)	112.14(12)
C(8)-C(12)-C(14)	112.35(11)	C(13)-C(12)-C(14)	110.86(12)
C(6C)-C(1A)-C(7A)	112.3(4)	C(6C)-C(1A)-C(2A)	89.7(4)
C(7A)-C(1A)-C(2A)	110.9(3)	C(6C)-C(1A)-C(6A)	21.3(3)
C(7A)-C(1A)-C(6A)	109.1(3)	C(2A)-C(1A)-C(6A)	109.8(3)
C(6C)-C(1A)-C(2C)	109.4(4)	C(7A)-C(1A)-C(2C)	110.7(4)
C(2A)-C(1A)-C(2C)	22.3(3)	C(6A)-C(1A)-C(2C)	127.5(4)
C(1A)-C(2A)-C(3A)	111.0(5)	C(4A)-C(3A)-C(2A)	111.7(6)
C(3A)-C(4A)-C(5A)	110.3(8)	C(6A)-C(5A)-C(4A)	111.4(6)
C(5A)-C(6A)-C(1A)	111.6(6)	C(8A)-C(7A)-C(1A)	128.50(12)
C(7A)-C(8A)-C(9A)	119.49(11)	C(7A)-C(8A)-C(12A)	123.78(12)
C(9A)-C(8A)-C(12A)	116.72(11)	O(2A)-C(9A)-N(1A)	121.45(12)
O(2A)-C(9A)-C(8A)	121.71(12)	N(1A)-C(9A)-C(8A)	116.83(11)
N(1A)-C(10A)-C(11A)	112.08(11)	O(1A)-C(11A)-C(10A)	110.57(11)
C(8A)-C(12A)-C(13A)	111.95(12)	C(8A)-C(12A)-C(14A)	112.03(12)
C(13A)-C(12A)-C(14A)	111.35(13)	C(3C)-C(2C)-C(1A)	112.5(7)
C(4C)-C(3C)-C(2C)	109.8(7)	C(5C)-C(4C)-C(3C)	112.7(9)
C(4C)-C(5C)-C(6C)	110.9(8)	C(1A)-C(6C)-C(5C)	111.2(7)

Symmetry transformations used to generate equivalent atoms.

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for *(E)*-**478**. The anisotropic displacement factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
O(1)	50(1)	20(1)	44(1)	1(1)	5(1)	-4(1)
O(2)	40(1)	29(1)	28(1)	-2(1)	2(1)	-1(1)
O(1A)	38(1)	31(1)	36(1)	0(1)	18(1)	2(1)
O(2A)	50(1)	21(1)	51(1)	3(1)	20(1)	5(1)
N(1)	38(1)	19(1)	28(1)	-2(1)	3(1)	-4(1)
N(1A)	34(1)	18(1)	33(1)	-2(1)	12(1)	4(1)
C(1)	41(1)	48(1)	27(1)	3(1)	4(1)	-14(1)
C(2)	36(1)	66(1)	73(1)	-35(1)	-1(1)	4(1)
C(3)	49(1)	67(1)	100(2)	-47(1)	-12(1)	8(1)
C(4)	43(1)	46(1)	82(1)	-4(1)	-10(1)	-10(1)
C(5)	35(1)	51(1)	50(1)	0(1)	2(1)	-2(1)
C(6)	42(1)	41(1)	40(1)	-2(1)	2(1)	4(1)
C(7)	41(1)	42(1)	26(1)	4(1)	4(1)	-10(1)
C(8)	34(1)	28(1)	28(1)	1(1)	8(1)	-1(1)
C(9)	33(1)	22(1)	30(1)	0(1)	11(1)	-2(1)
C(10)	32(1)	27(1)	29(1)	-2(1)	4(1)	-2(1)
C(11)	31(1)	41(1)	29(1)	-5(1)	2(1)	0(1)
C(12)	39(1)	31(1)	28(1)	2(1)	11(1)	-1(1)
C(13)	49(1)	48(1)	41(1)	5(1)	21(1)	-3(1)
C(14)	67(1)	48(1)	38(1)	13(1)	15(1)	19(1)
C(1A)	35(1)	41(1)	35(1)	7(1)	12(1)	9(1)
C(2A)	34(3)	70(4)	40(2)	1(3)	3(2)	15(3)
C(3A)	32(3)	90(6)	50(2)	13(4)	5(2)	22(4)
C(4A)	70(6)	63(5)	51(4)	15(3)	25(4)	39(4)
C(5A)	50(4)	60(3)	43(3)	3(2)	10(2)	23(2)
C(6A)	43(3)	45(3)	39(3)	-1(2)	14(2)	13(2)
C(7A)	36(1)	35(1)	30(1)	4(1)	12(1)	4(1)
C(8A)	33(1)	26(1)	27(1)	-1(1)	8(1)	0(1)
C(9A)	33(1)	23(1)	25(1)	-1(1)	4(1)	2(1)
C(10A)	30(1)	25(1)	32(1)	-3(1)	9(1)	1(1)
C(11A)	30(1)	38(1)	30(1)	-5(1)	10(1)	-1(1)
C(12A)	42(1)	34(1)	27(1)	4(1)	11(1)	5(1)
C(13A)	55(1)	57(1)	31(1)	7(1)	1(1)	7(1)
C(14A)	61(1)	45(1)	44(1)	7(1)	21(1)	-8(1)
C(2C)	36(3)	63(4)	53(3)	-4(4)	17(2)	1(3)
C(3C)	39(3)	70(5)	74(4)	1(4)	21(3)	8(3)
C(4C)	57(6)	51(5)	96(8)	9(5)	42(5)	16(4)
C(5C)	50(6)	66(7)	120(10)	-37(7)	39(7)	8(4)
C(6C)	44(4)	63(6)	100(7)	-31(5)	29(5)	2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for *(E)*-**478**.

	x	y	z	U(eq)
H(2)	4874	1703	2110	40
H(1A)	4814	-753	2701	40
H(1E)	1680	-422	-2286	47
H(2E)	1928	-2853	-1348	73
H(2B)	2334	-2542	-2049	73
H(3A)	1108	-2729	-2962	93
H(3B)	1238	-4082	-2440	93
H(4A)	-68	-3218	-2619	74
H(4B)	383	-3285	-1717	74
H(5A)	-265	-1194	-1965	56
H(5B)	164	-880	-2651	56
H(6A)	959	-1083	-1037	51
H(6B)	819	310	-1522	51
H(7)	2441	-618	-660	45
H(10A)	4780	1223	579	36
H(10B)	4788	-356	811	36
H(11A)	3807	1700	1242	42
H(11B)	3697	110	1398	42
H(12)	2609	771	-2440	39
H(13A)	4022	696	-2024	66
H(13B)	4018	2257	-1758	66
H(13C)	3709	1862	-2657	66
H(14A)	2450	3132	-2623	76
H(14B)	2720	3376	-1703	76
H(14C)	1906	2594	-2075	76
H(1A1)	1417	339	5453	44
H(2A1)	753	630	4136	59
H(2A2)	1197	2056	4105	59
H(3A1)	-99	2502	4256	70
H(3A2)	56	1551	5012	70
H(4A1)	197	3830	5422	71
H(4A2)	826	4112	4912	71
H(5A1)	1531	3795	6211	61
H(5A2)	1093	2368	6252	61
H(6A1)	2374	1944	6088	50
H(6A2)	2203	2882	5326	50
H(7A)	2381	653	4382	39
H(10C)	4792	-1205	4449	34
H(10D)	4727	282	4064	34
H(11C)	3828	-2047	3372	39
H(11D)	3717	-554	2992	39
H(12A)	2440	-669	6236	41
H(13D)	3520	-1715	7051	74
H(13E)	3854	-550	6584	74
H(13F)	3888	-2116	6338	74
H(14D)	1786	-2531	5525	73

H(14E)	2288	-3037	6359	73
H(14F)	2615	-3300	5603	73
H(2C1)	915	1335	4012	60
H(2C2)	719	-76	4380	60
H(3C1)	-328	1554	4300	72
H(3C2)	33	1072	5180	72
H(4C1)	425	3566	4516	77
H(4C2)	-84	3462	5154	77
H(5C1)	1014	2716	6071	91
H(5C2)	1209	4140	5714	91
H(6C1)	1910	2983	4898	80
H(6C2)	2286	2549	5782	80
H(1)	3674(8)	628(16)	4527(8)	27(4)
H(2A)	3716(9)	-662(17)	-148(8)	36(4)

Appendix 2. X-Ray crystallographic Data for *syn*-3-[2-(Benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one 572

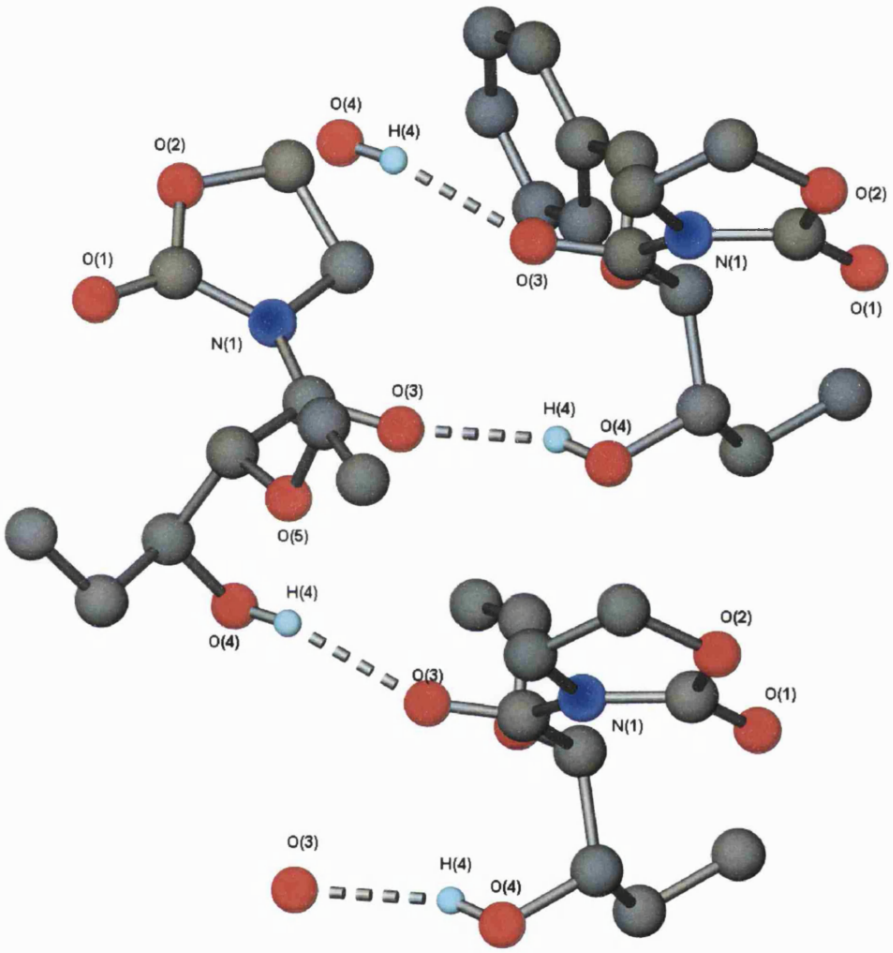

Table 1. Crystal data and structure refinement for *syn*-**572**.

Identification code	k03sdb01
Empirical formula	$C_{15}H_{19}NO_5$
Formula weight	293.31
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 12.5110(2)Å $\alpha = 90^\circ$
	b = 6.22300(10)Å $\beta = 95.8610(10)^\circ$
	c = 18.4300(4)Å $\gamma = 90^\circ$
Volume	1427.38(4) $Å^3$
Z	4
Density (calculated)	1.365 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	624
Crystal size	0.08 x 0.03 x 0.03 mm
Theta range for data collection	3.86 to 27.46°
Index ranges	-16<=h<=16; -8<=k<=8; -23<=l<=23
Reflections collected	23564
Independent reflections	3239 [R(int) = 0.0769]
Completeness to theta = 27.46°	99.3%
Absorption correction	None
Max. and min. transmission	0.9969 and 0.9918
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3239 / 0 / 264
Goodness-of-fit on F^2	1.030
Final R indices [I>2□(I)]	$R_1 = 0.0399$, $wR_2 = 0.0890$
R indices (all data)	$R_1 = 0.0627$, $wR_2 = 0.0996$
Extinction coefficient	0.024(3)
Largest diff. peak and hole	0.203 and –0.240 $eÅ^{-3}$

Hydrogen bonds [Å and °].

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)
O(4)-H(4)	0.8400	2.1001	157.70	2.8941

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for *syn*-**572**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3970(1)	168(2)	1228(1)	38(1)
O(2)	4796(1)	2220(2)	463(1)	42(1)
O(3)	7168(1)	-942(2)	2060(1)	39(1)
O(4)	5906(1)	-5258(2)	1957(1)	36(1)
O(5)	5873(1)	-1951(1)	3104(1)	31(1)
N(1)	5832(1)	268(2)	1262(1)	28(1)
C(1)	4786(1)	819(2)	1018(1)	30(1)
C(2)	5884(1)	2912(3)	385(1)	42(1)
C(3)	6596(1)	1344(3)	831(1)	42(1)
C(4)	6206(1)	-779(2)	1902(1)	28(1)
C(5)	5395(1)	-1715(2)	2382(1)	26(1)
C(6)	5022(1)	-3945(2)	2105(1)	28(1)
C(7)	4328(1)	-5056(2)	2625(1)	33(1)
C(8)	3387(1)	-3722(3)	2824(1)	40(1)
C(9)	5939(1)	24(2)	3499(1)	35(1)
C(10)	6236(1)	-425(2)	4291(1)	29(1)
C(11)	6827(1)	1073(3)	4723(1)	43(1)
C(12)	7101(1)	690(3)	5462(1)	50(1)
C(13)	6798(1)	-1172(3)	5770(1)	49(1)
C(14)	6212(1)	-2685(3)	5349(1)	46(1)
C(15)	5925(1)	-2300(2)	4616(1)	35(1)

Table 3. Bond lengths [Å] and angles [°] for *syn*-**572**.

O(1)-C(1)	1.1989(16)	C(7)-C(8)	1.516(2)
O(2)-C(1)	1.3458(16)	C(7)-H(7A)	1.000(16)
O(2)-C(2)	1.449(2)	C(7)-H(7B)	0.993(16)
O(3)-C(4)	1.2134(16)	C(8)-H(8A)	0.968(18)
O(4)-C(6)	1.4228(16)	C(8)-H(8B)	0.99(2)
O(4)-H(4)	0.8400	C(8)-H(8C)	0.993(17)
O(5)-C(5)	1.4095(15)	C(9)-C(10)	1.496(2)
O(5)-C(9)	1.4269(16)	C(9)-H(9A)	0.973(17)
N(1)-C(1)	1.3830(18)	C(9)-H(9B)	0.977(17)
N(1)-C(4)	1.3869(17)	C(10)-C(15)	1.385(2)
N(1)-C(3)	1.4646(18)	C(10)-C(11)	1.388(2)
C(2)-C(3)	1.507(2)	C(11)-C(12)	1.390(2)
C(2)-H(2A)	0.944(17)	C(11)-H(11)	0.96(2)
C(2)-H(2B)	0.984(16)	C(12)-C(13)	1.360(3)
C(3)-H(3A)	0.942(17)	C(12)-H(12)	0.91(2)
C(3)-H(3B)	0.946(19)	C(13)-C(14)	1.382(2)
C(4)-C(5)	1.5269(19)	C(13)-H(13)	0.98(2)
C(5)-C(6)	1.5352(18)	C(14)-C(15)	1.383(2)
C(5)-H(5)	0.970(14)	C(14)-H(14)	1.00(2)
C(6)-C(7)	1.523(2)	C(15)-H(15)	0.963(16)
C(6)-H(6)	1.015(13)		

C(1)-O(2)-C(2)	110.41(11)	O(3)-C(4)-C(5)	122.10(12)
C(6)-O(4)-H(4)	109.5	N(1)-C(4)-C(5)	119.04(11)
C(5)-O(5)-C(9)	112.89(10)	O(5)-C(5)-C(4)	110.08(11)
C(1)-N(1)-C(4)	128.21(11)	O(5)-C(5)-C(6)	107.76(10)
C(1)-N(1)-C(3)	110.99(11)	C(4)-C(5)-C(6)	110.46(10)
C(4)-N(1)-C(3)	119.63(12)	O(5)-C(5)-H(5)	111.9(8)
O(1)-C(1)-O(2)	122.55(13)	C(4)-C(5)-H(5)	109.2(8)
O(1)-C(1)-N(1)	128.36(12)	C(6)-C(5)-H(5)	107.4(8)
O(2)-C(1)-N(1)	109.05(12)	O(4)-C(6)-C(7)	111.32(11)
O(2)-C(2)-C(3)	105.22(12)	O(4)-C(6)-C(5)	111.53(11)
O(2)-C(2)-H(2A)	108.0(10)	C(7)-C(6)-C(5)	112.00(11)
C(3)-C(2)-H(2A)	113.8(10)	O(4)-C(6)-H(6)	100.7(7)
O(2)-C(2)-H(2B)	107.4(9)	C(7)-C(6)-H(6)	110.2(7)
C(3)-C(2)-H(2B)	112.4(9)	C(5)-C(6)-H(6)	110.5(7)
H(2A)-C(2)-H(2B)	109.7(13)	C(8)-C(7)-C(6)	114.22(12)
N(1)-C(3)-C(2)	102.14(12)	C(8)-C(7)-H(7A)	109.9(8)
N(1)-C(3)-H(3A)	109.7(11)	C(6)-C(7)-H(7A)	107.9(9)
C(2)-C(3)-H(3A)	114.1(10)	C(8)-C(7)-H(7B)	110.8(9)
N(1)-C(3)-H(3B)	109.9(11)	C(6)-C(7)-H(7B)	107.0(9)
C(2)-C(3)-H(3B)	110.7(11)	H(7A)-C(7)-H(7B)	106.8(12)
H(3A)-C(3)-H(3B)	110.1(15)	C(7)-C(8)-H(8A)	110.8(10)
O(3)-C(4)-N(1)	118.85(12)	C(7)-C(8)-H(8B)	110.2(10)

H(8A)-C(8)-H(8B)	106.6(14)	C(10)-C(11)-H(11)	117.1(11)
C(7)-C(8)-H(8C)	110.9(9)	C(12)-C(11)-H(11)	122.2(11)
H(8A)-C(8)-H(8C)	108.7(14)	C(13)-C(12)-C(11)	120.22(15)
H(8B)-C(8)-H(8C)	109.5(14)	C(13)-C(12)-H(12)	120.8(12)
O(5)-C(9)-C(10)	109.47(11)	C(11)-C(12)-H(12)	119.0(12)
O(5)-C(9)-H(9A)	112.1(9)	C(12)-C(13)-C(14)	120.04(15)
C(10)-C(9)-H(9A)	110.5(9)	C(12)-C(13)-H(13)	122.1(11)
O(5)-C(9)-H(9B)	109.4(10)	C(14)-C(13)-H(13)	117.8(12)
C(10)-C(9)-H(9B)	109.9(10)	C(15)-C(14)-C(13)	120.01(16)
H(9A)-C(9)-H(9B)	105.4(13)	C(15)-C(14)-H(14)	120.3(11)
C(15)-C(10)-C(11)	118.34(14)	C(13)-C(14)-H(14)	119.7(11)
C(15)-C(10)-C(9)	121.73(12)	C(14)-C(15)-C(10)	120.75(14)
C(11)-C(10)-C(9)	119.93(13)	C(14)-C(15)-H(15)	122.3(9)
C(10)-C(11)-C(12)	120.63(16)	C(10)-C(15)-H(15)	116.9(9)

Symmetry transformations used to generate equivalent atoms.

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for *syn*-**572**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	31(1)	44(1)	38(1)	10(1)	2(1)	4(1)
O(2)	53(1)	39(1)	34(1)	13(1)	9(1)	8(1)
O(3)	29(1)	39(1)	48(1)	-3(1)	-2(1)	2(1)
O(4)	40(1)	32(1)	34(1)	-10(1)	-2(1)	7(1)
O(5)	45(1)	21(1)	24(1)	-2(1)	-5(1)	4(1)
N(1)	31(1)	24(1)	30(1)	2(1)	9(1)	3(1)
C(1)	39(1)	26(1)	26(1)	1(1)	5(1)	7(1)
C(2)	62(1)	35(1)	31(1)	4(1)	19(1)	0(1)
C(3)	45(1)	33(1)	50(1)	5(1)	26(1)	3(1)
C(4)	31(1)	21(1)	31(1)	-4(1)	2(1)	3(1)
C(5)	32(1)	23(1)	23(1)	1(1)	-1(1)	4(1)
C(6)	34(1)	24(1)	25(1)	-3(1)	-2(1)	3(1)
C(7)	43(1)	23(1)	32(1)	-1(1)	1(1)	-2(1)
C(8)	41(1)	38(1)	40(1)	-1(1)	7(1)	-3(1)
C(9)	53(1)	22(1)	30(1)	-4(1)	2(1)	-2(1)
C(10)	32(1)	29(1)	28(1)	-6(1)	4(1)	-1(1)
C(11)	51(1)	39(1)	38(1)	-11(1)	5(1)	-13(1)
C(12)	41(1)	66(1)	40(1)	-24(1)	-2(1)	-12(1)
C(13)	48(1)	71(1)	27(1)	-4(1)	-1(1)	2(1)
C(14)	57(1)	51(1)	32(1)	4(1)	7(1)	-5(1)
C(15)	38(1)	37(1)	30(1)	-5(1)	4(1)	-7(1)

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An (*E*)-selective synthesis of trisubstituted (*E*)-α,β-unsaturated acid derivatives†

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Potassium alkoxides of *N*-acyloxazolidin-2-one derived *syn*-aldolates undergo a novel tandem intramolecular cyclisation elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e., which may be converted into their corresponding acids or oxazolines in good yield.

There are currently few general methods available for the diastereoselective synthesis of (*E*)-α,β-unsaturated acids/esters/amides that are substituted at both their α- and β-positions.[1] These types of trisubstituted α,β-unsaturated acid derivatives are important targets because they serve as versatile substrates for a wide range of synthetic methodology,[2] and for the construction of a wide range of natural products.[3,4] Previously, (*E*)-acid derivatives of this type have been prepared using Wittig,[3] or Horner–Emmons[4] methodology, however alternative diastereoselective protocols employing excess SmI_2[5] or $CrCl_2$[6] to effect the reductive elimination of α-halo-β-hydroxy-esters or amides have recently been described. We now report an alternative approach towards this class of acid fragment, that employs *syn*-β-hydroxy-*N*-acyloxazolidin-2-ones as substrates for a novel intramolecular cyclisation/elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e.

In the course of our synthetic studies we prepared nine racemic *syn*-aldolates **2a–i** in high d.e. *via* reaction of the boron enolates of *N*-acyloxazolidin-2-ones **1a–d** (**1a** R = Me; **1b** R = ^{i}Pr; **1c** R = Ph, **1d** R = $PhCH_2$–) with a series of aldehydes according to well established literature precedent.[7] It was found that treatment of these *syn*-aldolates **2a–h** with 1.5 equivalents of KHMDS in THF at −78 °C resulted in a clean elimination reaction to afford the corresponding α,β-unsaturated amides (*E*)-**3a–h** in 67–99% isolated yield, and in >90% d.e.[8] in all cases.[9] It is noteworthy that this simple elimination methodology is general in scope, with linear and branched R-substituents being tolerated at the α-position of the *syn*-aldolates **2a–h**, and with aliphatic, unsaturated, and aromatic (neutral and electron rich) R_1-substituents being tolerated at the β-position (Scheme 1, Table 1). The only limitation of this methodology occurred during elimination of **2i** (R = Ph, R_1 = Et) which gave **3i** in a lower 47% isolated yield as a result of a competing *retro*-aldol reaction which gave (*N*-phenylacetyl)oxazolidin-2-one **1c** (R = Ph) and propionaldehyde (not isolated) as competing side-products in 32% yield.

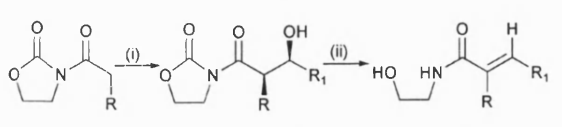
It is well known that sterically unhindered *N*-acyloxazolidin-2-ones can undergo endocyclic ring cleavage *via* either inter- or intramolecular attack of nucleophiles at their oxazolidin-2-one carbonyl groups.[10] Consequently, it was proposed that the high diastereoselectivities observed for the formation of (*E*)-α,β-unsaturated amides **3a–h** in this reaction could be explained by invoking an intramolecular endocyclic cleavage mechanism. Thus, potassium alkoxide **4** initially undergoes intramolecular attack at the oxazolidin-2-one carbonyl resulting in O–O carbonyl migration, to afford 1,3-oxazinane-2,4-dione alkoxide **5**. Subsequent anion equilibration of alkoxide **5** to enolate **6** would then enable stereoselective elimination of carbon dioxide to occur to afford the trisubstituted secondary amide (*E*)-**3** in high d.e. (Fig. 1).

It has been reported previously that reaction of the Zn enolate of α-bromo-*N*-acyl-oxazolidin-2-one **7** with benzaldehyde did not afford the expected aldolate product, but instead gave a mixture of rearranged 1,3-oxazinane-2,4-dione diastereoisomers **8** and **9** in good yield (Scheme 2).[11] Since this implied that Zn alkoxides of β-hydroxy-*N*-acyloxazolidin-2-ones underwent rearrangement to their corresponding 1,3-oxazinane-2,4-diones, we treated *syn*-aldolate **2f** with 10 mol% of Et_2Zn in CH_2Cl_2 at room temperature to cleanly afford its corresponding 1,3-oxazinane-2,4-dione **10** in 88% yield.[12] Subsequent treatment of **10** with KHMDS in THF at −78 °C gave (*E*)-**3f** in >90% d.e., thus providing good evidence that the potassium alkoxide of

Table 1 Synthesis of (*E*)-α,β-unsaturated amides **3a–h**

Entry	Aldolate	R	R_1	Product	d.e.[a]	% Yield[b]
1	**2a**	Me	Ph	**3a**	>95	89
2	**2b**	Me	Et	**3b**	>95	67
3	**2c**	$PhCH_2$–	$Me(CH_2)_6$–	**3c**	92	99
4	**2d**	^{i}Pr	cyclohexyl	**3d**	93	76
5	**2e**	^{i}Pr	(*E*)-Ph(CH=CH)–	**3e**	>95	95
6	**2f**	^{i}Pr	Et	**3f**	>95	99
7	**2g**	^{i}Pr	Ph	**3g**	92	94
8	**2h**	^{i}Pr	*p*-MeOPh–	**3h**	90	79
9	**2i**	Ph	Et	**3i**	>95	47

[a] All diastereoselectivities were determined *via* ^{1}H NMR spectroscopic analysis (300 MHz) of the crude reaction product. [b] Yields are for pure (*E*)-diastereoisomers isolated after chromatographic purification.



Scheme 1 *Reagents and conditions:* (i) 9-BBNTf, $^iPr_2NEt$, CH_2Cl_2, 0 → −78 °C; R_1CHO, CH_2Cl_2; (ii) KHMDS (1.5 eq.), THF, −78 °C.

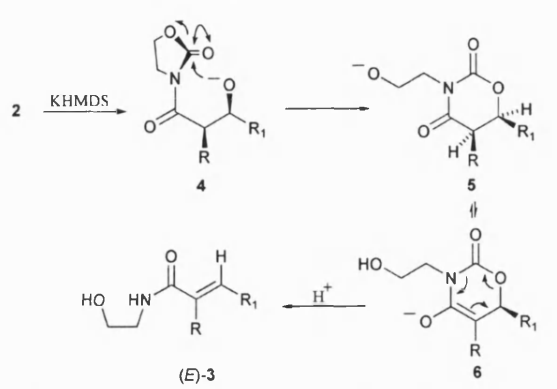


Fig. 1 Intramolecular cyclisation/elimination mechanism for the formation of (*E*)-α,β-unsaturated amides **3**.

† Electronic supplementary information (ESI) available: synthesis and spectroscopic details for compounds **3a** and **12a**. See http://www.rsc.org/suppdata/cc/b3/b304213h/

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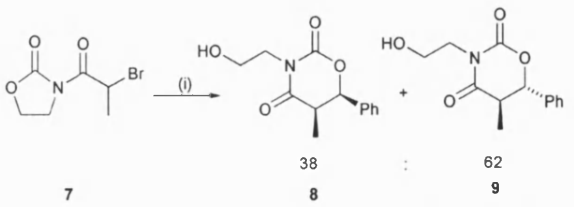
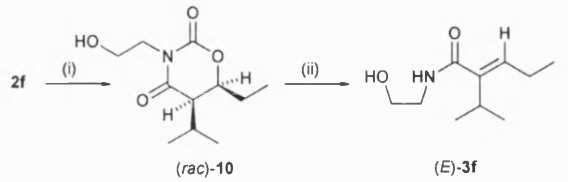


Scheme 2 *Reagents and conditions:* (i) Zn, THF, −78 °C, PhCHO.

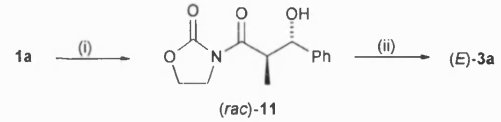


Scheme 3 *Reagents and conditions:* (i) Et_2Zn (10 mol%), CH_2Cl_2, 0 °C; (ii) KHMDS, THF, −78 °C.

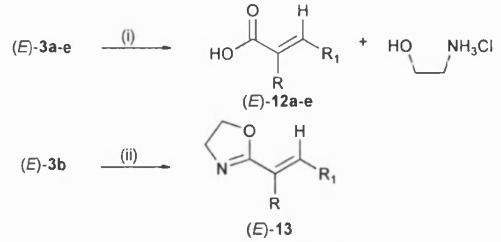
1,3-oxazinane-2,4-dione **5** is a key intermediate in controlling diastereoselectivity during stereoselective elimination of the potassium alkoxides of *syn*-aldolates **2a–h** (Scheme 3).

We next explored elimination of the corresponding *anti*-aldolate **11** which was prepared *via* treatment of **1a** with $MgCl_2$, TMSCl, Et_3N and benzaldehyde in EtOAc according to Evans' recently published procedure.[13] Treatment of *anti*-aldolate **11** with KHMDS in THF at −78 °C afforded amide (*E*)-**3a** in >95% d.e. identical to that observed previously for elimination of *syn*-**2a** under the same conditions (Scheme 4). This is consistent with the key elimination step of both *syn*-**2a** and *anti*-**11** occurring *via* an E1cB-type mechanism, to afford a common enolate intermediate **6** that decomposes to afford α,β-unsaturated amide (*E*)-**3a** in high d.e.

In order to demonstrate the synthetic utility of this methodology, a range of diastereomerically pure trisubstituted secondary amides (*E*)-**3a–e** were hydrolysed to their parent acids **12a–e** by refluxing in 6 M HCl for two hours in 91–99% yield.† Importantly, no evidence of any products resulting from double bond migration were observed in the ^1H NMR spectra of the crude hydrolysis products of **3a–e** (Scheme 5, Table 2, entries 1–5).[14] The potential synthetic versatility of this methodology arising from the presence of the *N*-hydroxyalkyl substituent of α,β-unsaturated amides **3a–e** was also demonstrated *via*



Scheme 4 *Reagents and conditions:* (i) $MgCl_2$, Et_3N, TMSCl, PhCHO, EtOAc, rt; (ii) KHMDS, THF, −78 °C.



Scheme 5 *Reagents and conditions:* (i) 6 M HCl, Δ; (ii) $SOCl_2$, rt.

Table 2 Yields of (*E*)-α,β-unsaturated acids **12a–e** and (*E*)-oxazoline **13**

Entry	Amide	R	R_1	Product	% Yield
1	**3a**	Me	Ph	**12a**	99
2	**3b**	Me	Et	**12b**	91
3	**3c**	$PhCH_2$–	$Me(CH_2)_6$–	**12c**	99
4	**3d**	^{i}Pr	cyclohexyl	**12d**	99
5	**3e**	^{i}Pr	(*E*)-Ph(CH=CH)–	**12e**	99
6	**3b**	Me	Et	**13**	88

conversion of **3b** to its corresponding trisubstituted-α,β-unsaturated oxazoline (*E*)-**13** on treatment with thionyl chloride in 88% yield (Scheme 5, Table 2, entry 6).[15]

In conclusion, we have demonstrated that treatment of easily prepared *N*-acyloxazolidone-*syn*-aldolates with KHMDS affords an alkoxide intermediate which undergoes a stereoselective base mediated elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e.

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Notes and references

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